

# THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY

## Sex through the ages: an endocrine perspective



Special  
features

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For mutual benefit  
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# A word from THE EDITOR...



Things are hotting up! Welcome to this summer issue dedicated to 'Sex through the ages'.

When encouraging students to pursue a scientific and/or clinical career in endocrinology, I often tell them that endocrine science and practice span the entire human life cycle, making endocrinology the most vibrant, inclusive and fascinating discipline in medicine. The field of reproductive endocrinology has witnessed exciting advances over recent years, and it is wonderful to see UK scientists and clinicians continuing to play a major role in ground-breaking developments.

The feature articles in this issue of *The Endocrinologist* cover many topical issues in this area. Raj Mathur gives us an insight into fertility preservation, discussing some fundamental principles and touching on what's on the horizon in this fast-moving area. Alex Comminos and Waljit Dhillon's excellent piece suggests that kisspeptin may be the master regulator of reproduction. They discuss their recent work revealing roles for kisspeptin in sexual and emotional behaviour.

Rod Mitchell focuses on endocrine disruption and male reproductive health, while Heather Blackmore highlights the importance of animal studies in uncovering mechanistic insights into how the maternal environment drives offspring phenotype. In addition, Channa Jayasena, Du Soon Sweet, Andrew Dwyer and Richard Quinton brilliantly summarise all you need to know about induction of spermatogenesis in men with gonadotrophin deficiency.

To gear you all up for summer, Gerard Conway has written from sunny Western Australia! He introduces a pregnancy audit for women with Turner syndrome and congenital adrenal hyperplasia, emphasising that there is much to learn about pregnancy outcomes in women with a variety of endocrine conditions. Finally, articles by Annice Mukherjee and Agnieszka Swiecicka shine a spotlight on challenging questions in reproductive hormone replacement therapy.

We had a heart-warming boost in our online readership for the last edition and I hope this promising trajectory continues!

Enjoy the summer. With warmest good wishes

AMIR SAM

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[www.endocrinology.org/endocrinologist](http://www.endocrinology.org/endocrinologist)

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**Become a contributor...** Contact the Editorial office at [endocrinologist@endocrinology.org](mailto:endocrinologist@endocrinology.org)

The Society welcomes news items, contributions, article suggestions and letters to the Editor. We would also like to hear your feedback on this issue of the magazine.

Deadline for news items for the Autumn 2018 issue: **10 July 2018**.

Front cover image ©Shutterstock



## NEW PREMISES FOR SOCIETY HQ

The Society offices moved in May to a new location in north Bristol. The new office building – named Starling House – is larger to accommodate the expanding activities of the Society and particularly its trading subsidiary, Bioscientifica, within publishing, events and association management.

The move represents an exciting new phase for the SfE Group in the development of the organisation.

While our email and phone contact details remain the same, please note our new postal address in the adjacent column!

## NEW SOCIETY ADDRESS

Society For Endocrinology  
Starling House  
1600 Bristol Parkway North  
Bristol BS34 8YU

## MAKE YOUR MEDAL NOMINATIONS SOON

Help us recognise excellence in endocrinology: nominations for recipients of the Society's seven medals must be submitted by **2 July**.

Full details and the nomination forms can be found at [www.endocrinology.org/grants-and-awards/prizes-and-awards/medals](http://www.endocrinology.org/grants-and-awards/prizes-and-awards/medals).

## FUNDS FOR CONFERENCE ATTENDANCE

Are you attending SfE BES 2018 or an overseas endocrine meeting before the end of year? You may be eligible for a Society Travel Grant. Applications must be received by **15 August**. For details and to apply, visit

[www.endocrinology.org/grants-and-awards](http://www.endocrinology.org/grants-and-awards).

## REWARDING UNDERGRADUATE ACHIEVEMENT

Apply now for the Society's Undergraduate Achievement Award, which recognises and promotes excellence in the study of endocrinology. Your department would receive £300 per year for 3 years to reward outstanding undergraduates for excellence in their endocrine-related studies.

Applications close on **31 July 2018**.

Find out more at:

[www.endocrinology.org/grants-and-awards](http://www.endocrinology.org/grants-and-awards).

## HELP DRIVE ENDOCRINOLOGY FORWARD

Make your nominations now to fill vacancies for Endocrine Network convenors, which will arise at the end of 2018.

The Endocrine Networks each provide a dedicated forum in a major area of endocrinology and enable members with similar interests to come together, share best practice and ideas, and actively promote collaboration with other learned organisations, thereby increasing the profile of endocrinology as a specialty.

If you would like a turn in the driving seat, full details and a nomination form are at [www.endocrinology.org/membership/endocrine-networks](http://www.endocrinology.org/membership/endocrine-networks).

## DON'T MISS THE SOCIETY'S LATEST BLOG POSTS

Visit The Endocrine Post at [www.endocrinologyblog.org](http://www.endocrinologyblog.org) for the latest news, views and interviews with leading endocrinologists.

## NOMINATIONS CLOSING FOR COMMITTEE MEMBERS

Don't forget! Vacancies will arise at the end of the year on the following Society committees:

- Clinical
- Nurse
- Corporate Liaison
- Programme
- Finance
- Public Engagement
- Nominations
- Science

Send your nomination forms to the Society office by **29 June**.

Full details and forms can be found at [www.endocrinology.org/about-us/governance/call-for-nominations](http://www.endocrinology.org/about-us/governance/call-for-nominations).

## WITH REGRET

We are sorry to announce the death of Senior Member and co-discoverer of aldosterone, Hilary Drane née Grundy. A full obituary will appear in the next issue of *The Endocrinologist*.

## HELP IMPROVE SCIENCE REPORTING IN THE MEDIA

Become a Society Media Ambassador and share your expertise to improve accuracy in media coverage of endocrine topics.

Find out more at [www.endocrinology.org/outreach/public-engagement](http://www.endocrinology.org/outreach/public-engagement).



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## SOCIETY CALENDAR

11 September 2018  
**13TH INTERNATIONAL WORKSHOP ON RESISTANCE TO THYROID HORMONE**  
Doorn, The Netherlands

15 September 2018  
**41ST ANNUAL MEETING OF THE EUROPEAN THYROID ASSOCIATION**  
Newcastle upon Tyne

24 September 2018  
**PITUITARY MASTERCLASS 2018**  
London

19–21 November 2018  
**SfE BES 2018**  
Glasgow

[www.endocrinology.org/events](http://www.endocrinology.org/events) for full details



## GRANT AND PRIZE DEADLINES

13 June 2018  
**REGIONAL CLINICAL CASES MEETING GRANTS**

1 June–31 July 2018  
**UNDERGRADUATE ACHIEVEMENT AWARD**

15 August 2018  
**TRAVEL GRANT**

26 September 2018  
**PUBLIC ENGAGEMENT GRANT**

27 September 2018  
**SOCIETY FOR ENDOCRINOLOGY BES REGISTRATION GRANTS**

31 October 2018  
**PRACTICAL SKILLS GRANT**

28 November 2018  
**EARLY CAREER GRANT**

28 November 2018  
**EQUIPMENT GRANT**

Ongoing applications  
**ENDOCRINE NETWORK GRANTS**

[www.endocrinology.org/grants](http://www.endocrinology.org/grants) for full details of all Society grants and prizes



## SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

Society members have free access to the current content of *Journal of Endocrinology*, *Journal of Molecular Endocrinology*, *Endocrine-Related Cancer* and *Clinical Endocrinology* via the members' area on the Society home page, [www.endocrinology.org](http://www.endocrinology.org). *Endocrine Connections* and *Endocrinology, Diabetes & Metabolism Case Reports*, the Society-endorsed case reports publication, are open access (OA) and free to all.



### JOURNAL OF ENDOCRINOLOGY

#### Another good reason to soak up the sunshine

Vitamin D is essential for optimal neurodevelopment and subsequent function, as reflected by the high level of expression of vitamin D receptors in fetal brain. Recent evidence also points to an association between vitamin D deficiency and autism spectrum disorder (ASD) development.

So, to determine the link between early life vitamin D status and ASD, Yates and colleagues modelled vitamin D deficiency during gestation and lactation in rats, and assessed maternal care, offspring neurodevelopmental markers, ultrasonic vocalisations and adult behavioural outcomes, including social, cognitive and affective-like behaviours.

Their findings highlight the importance of vitamin D in both the mother and her offspring. Dams deficient in vitamin D spent less time grooming their pups, which can have long term effects on the offspring in addition to those caused by vitamin D deficiency. Offspring born to vitamin D deficient dams not only displayed an ASD-like phenotype but also had marked changes in brain anatomy previously shown to be associated with autism.

This study highlights the importance of monitoring vitamin D levels in pregnant women and providing appropriate supplementation, as it can have long-lasting consequences for her offspring.

Read the full article in *Journal of Endocrinology* **237** 73–85

### JOURNAL OF MOLECULAR ENDOCRINOLOGY

#### Hepcidin: a drug target to prevent postmenopausal osteoporosis?

Lack of oestrogen is considered to be the main reason for postmenopausal osteoporosis. However, some studies have also proposed that iron accumulation can accelerate osteoporosis after menopause.

Hepcidin is an endogenous hormone which regulates iron in the body. Zhang *et al.* genetically modified expression of hepcidin, with the aim of modulating iron

status in a mouse model. They monitored any effects on bone loss in the mice. Results showed that hepcidin levels were negatively correlated with bone loss.

These results are further evidence of the 'iron accumulation' hypothesis, which suggests that high iron levels are risk factors for osteoporosis, and highlight hepcidin as a potential drug target for prevention of postmenopausal osteoporosis.

Read the full article in *Journal of Molecular Endocrinology* **60** 299–308

### ENDOCRINE-RELATED CANCER

#### Biomarker prediction of ER-negative breast cancer chemotherapy outcome

Breast cancer patients whose tumours are oestrogen receptor (ER)-negative are more likely to have poorer outcomes than those with ER-positive tumours. These patients are often treated with standard chemotherapy regimens, rather than the hormonal and targeted treatments used for ER-positive patients.

Chen *et al.* obtained large published datasets of drug response and gene expression profiles (breast cancer patient cohorts, plus *in vitro* studies of cancer cell lines). They then used these to develop genomic biomarker signatures for

the agents paclitaxel, 5-fluorouracil, cyclophosphamide and doxorubicin, which are commonly used as adjuvant chemotherapies for ER-negative patients. These models were subsequently validated in independent patient datasets.

The authors hope that their proposed biomarker panels could be used to predict which patients are most likely to respond to a particular agent. This would facilitate personalised treatment decisions, rather than agents being used in a 'trial and error' manner.

Read the full article in *Endocrine-Related Cancer* **25** 595–605

## ENDOCRINE HIGHLIGHTS

A summary of papers from around the endocrine community that have got you talking.

#### FGF21 as an endocrine inhibitor of alcohol appetite in humans

The biology that motivates us to consume alcohol is incompletely understood. This has been a limiting factor in the design of pharmacological interventions to control alcohol use in at-risk populations. Alcohol consumption has been shown to increase levels of the hormone fibroblast growth factor 21 (FGF21) in human blood. Moreover, high levels of FGF21 reduce sweet and alcohol intake in mice, suggesting a feedback loop in the liver to limit alcohol consumption.

To test this, Søberg *et al.* measured plasma levels of FGF21 in humans after consumption of ethanol equivalent to 2.5 standard drinks acutely, or 3 days of binge drinking at Oktoberfest. Both resulted in increased circulating FGF21, which was present even at 32 hours after consuming the last unit of alcohol. Mice given recombinant human FGF21 showed reduced *ad libitum* alcohol intake.

The authors concluded that circulating FGF21 may be a liver-derived inhibitor of alcohol intake in humans, akin to gut peptides that reduce food intake after meals.

Read the full article in *Molecular Metabolism* **11** 96–103



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## CLINICAL ENDOCRINOLOGY

### Long-term growth hormone safety: a combined registry analysis

Whilst GH replacement is no longer a hot topic, safety issues remain in the product information literature, which cause concern, in particular for those who have survived childhood cancer.

Stochholm and Kiess report on an impressive number of patients (>150,000) taken from post-marketing surveillance databases. Studies were not pooled but reported per individual database and numbers were still impressive. For example, Pfizer databases include >83,000 children and >16,000 adults, and those held by Eli Lilly have 22,929 children and >10,000 adults.

The observational data showed that GH was not associated with an increased risk of new malignancy, leukaemia, non-leukaemic extracranial tumours or recurrence of intracranial malignancy in patients without risk factors during GH treatment. There was evidence of an increased incidence of a second neoplasm in children previously treated for cancer (3.8% and 6% in two of the studies reported), particularly if they had received radiation therapy for a central nervous system tumour. It remains likely that factors other than GH treatment,

including genetic predisposition, high grade/metastatic disease, high dose chemotherapy and era of treatment, are the reasons for the second malignancy. Second malignancy was well reported in this patient cohort and there were no case controls. A recent meta-analysis reported no increased risk for secondary malignancies among adults with hypopituitarism treated with GH. There did seem to be an increased risk of type 2 diabetes in obese adults on GH.

The authors suggest there are insufficient data to comment on an increased rate of growth for craniopharyngioma and non-functioning pituitary adenoma. Whilst no risk of regrowth was noted, these are slow-growing tumours and it was felt that more than 20 years of follow up was needed to answer this question.

These data are reassuring and there is no evidence to suggest that GH replacement should be withheld on safety grounds. The authors dedicated the manuscript to Jens Sandahl Christiansen, a giant in the field of GH physiology and study of metabolism, who is fondly remembered by many.

Read the full article in *Clinical Endocrinology* **88** 515–528

## ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

### A neglected presentation of thyrotoxicosis

Thyrotoxicosis is associated with cardiac dysfunction: more commonly, left ventricular dysfunction. However, in recent years, there have been more cases reported regarding right ventricular dysfunction, often associated with pulmonary hypertension, in patients with thyrotoxicosis.

Shalini Singarayar *et al.* present the largest case series so far, in an attempt to establish the common clinical features, echocardiographic parameters and clinical course of right ventricular dysfunction and thyrotoxicosis. The echocardiography for almost all cases revealed dilated right atrial and/

or ventricular chambers, with elevated pulmonary artery pressure, but such parameters can be resolved by rendering the patients euthyroid.

Right ventricular dysfunction and pulmonary hypertension are not well-recognised complications of thyrotoxicosis, but they can be reversed with early recognition and treatment of thyrotoxicosis. Signs and symptoms of right ventricular dysfunction should be sought in all patients with newly diagnosed thyrotoxicosis, and prompt restoration of euthyroidism is warranted in affected patients before development of overt right heart failure.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* EDM180012

## ENDOCRINE CONNECTIONS

### Lipid profile and blood pressure in Cushing's disease

Hypertension is present in 70–85% of adults with Cushing's disease, with chronic hypertension putting patients at increased risk of cardiovascular morbidity. Previous studies have suggested that hypertension in Cushing's disease may result, in part, from vascular remodelling. Hypertrophic changes in the morphology of small-resistance arteries (increased media-to-lumen ratio, media thickness and wall thickness) have been described in patients with the disease, and this has potentially been associated with aggregate low-density lipoprotein (LDL) uptake in vascular cells. However, the relationship between plasma lipids and hypertension in Cushing's disease has not been investigated.

Qin *et al.* evaluated the potential relationship between lipid profile and blood pressure in a retrospective study of 84 patients referred to Huashan Hospital (Shanghai, China) for evaluation and diagnosis of Cushing's disease. They found an independent association between low-density lipoprotein cholesterol (LDL-c) and systolic blood pressure in the patients. From their results, it is speculated that LDL-c may be a pathogenic factor for hypertension in these cases.

Read the full article in *Endocrine Connections* **7** 637–644



### Very-low-carb diet shows promise in type 1 diabetes

In results taken from an online patient survey, Lennerz *et al.* identified the potential for very-low-carbohydrate diets to improve blood sugar control in type 1 diabetes.

The survey respondents reported an average daily carbohydrate intake of 36g, or about 5% of total calories. (As a comparison, the American Diabetes Association recommends that about 45% of calories come from carbohydrates.) Respondents reported using lower-than-average doses of insulin, and reported positive measures of insulin sensitivity and cardiometabolic health, such as low triglyceride levels and high HDL cholesterol levels.

Safety concerns have been raised about very-low-carbohydrate diets in type 1 diabetes, in particular an increased risk of hypoglycaemia. However, the survey respondents reported rates of hospitalisation for hypoglycaemia (1%), diabetic ketoacidosis (2%) and other diabetes complications that were lower than those generally reported for type 1 diabetes populations. More than 80% of survey respondents were satisfied or very satisfied with their diabetes management. The researchers are now calling for controlled clinical trials of this approach.

Read the full article in *Pediatrics* doi:10.1542/peds.2017-3349

### Metabolic slowing and reduced oxidative damage with sustained caloric restriction

The notion that caloric restriction (CR) might extend lifespan is not a new one. In this intriguing study, Redman *et al.* sought to investigate the hypothesis that CR might reduce oxidative stress, and thus potentially slow the ageing process.

A total of 53 volunteers completed their 2-year programme, with the intervention group achieving an approximately 15% reduction in calorie intake (the target being a 25% reduction). The CR group achieved and maintained marked weight loss (mean 9kg per person), and were observed to have reduced levels of fasting insulin, leptin, and tri-iodothyronine and thyroxine, compared with the control group. The CR group's nighttime core body temperature, hypothesised to be a biomarker of ageing, also fell over the 2 years. Urinary excretion of F2-isoprostane, indicative of oxidative stress, declined significantly from baseline in the CR group too.

Whilst the authors stress that their findings do not extrapolate directly to longevity, they suggest that CR improves efficiency of energy utilisation, which might be a means to extend lifespan.

Read the full article in *Cell Metabolism* **27** 805–815.e4

# AN INSIGHT INTO FERTILITY PRESERVATION



WRITTEN BY RAJ MATHUR

The field of fertility preservation is an example of how advances in one area of clinical medicine can have a direct impact on the quality of care in another. It also shows some of the challenges when we attempt to work across traditional disciplines and boundaries. While everyone tries to do their best for the patient in front of them, awareness of options and ease of referral pathways can make all the difference to whether patients are offered, and take up, the option of preserving their fertility.

Fertility preservation applies to both men and women. We see individuals faced with the prospect of losing their fertility for medical reasons, as well as those who are medically well, but wish to take measures to preserve the option of parenthood at a later stage of their lives (so-called 'social fertility preservation').

While social egg freezing, in particular, has attracted a lot of media attention, the more immediate challenge for the NHS is to set up pathways for fertility preservation in individuals where either their diagnosis or their proposed treatment threatens harm to fertility, and time is of the essence.

## CASES WITH A MEDICAL NEED

The largest group of patients in this category are those diagnosed with cancer, who face the prospect of damage to their fertility as a result of chemotherapy, radiotherapy or surgery. As survival rates from cancer have improved, the quality of life for survivors has come into focus. It is known that cancer survivors rate loss of fertility as the most distressing outcome of cancer treatment.

There are also situations outside oncology where patients' fertility may be at risk, such as stem cell transplantation in individuals with sickle cell anaemia. Individuals transitioning from one gender to another may wish to retain the possibility of genetic parenthood.

The likelihood of damage is related to the age of the patient, and the type and dose of chemotherapy and radiotherapy. For instance, alkylating agents and pelvic radiotherapy present a high risk of leading to ovarian follicular depletion, while anthracyclines have a low risk. Abdomino-pelvic radiation in excess of 24 gray is associated with complete ovarian failure. Cranial radiotherapy can lead to impaired hypothalamo-pituitary-gonadal function, although the ovarian follicular pool may not be affected.

This means that the risk of subsequent infertility needs to be assessed on an individual basis for each patient. It is appropriate for fertility preservation to be discussed at an early stage of the treatment process. Whether or not it is offered as a treatment option depends on whether the cancer treatment is curative in intent, the risk to fertility from treatment, the fitness of the patient to undergo ovarian stimulation and egg retrieval and, finally, the possible effect of a delay in starting cancer treatment on the prognosis.

## OVARIAN STIMULATION

Within reproductive medicine, ovarian stimulation regimes now exist that can minimise the delay and risk associated with this process. Specifically, we now know that we can start ovarian stimulation at any point in the menstrual cycle, using the gonadotrophin-releasing hormone (GnRH) antagonist to prevent an endogenous luteinising hormone (LH) rise. In

women receiving GnRH antagonist, the pituitary retains its sensitivity to GnRH. This property allows us to use a single dose of GnRH agonist as a trigger for final follicular maturation in women on the antagonist. The agonist trigger causes an endogenous surge of LH (and follicle-stimulating hormone), which is sufficient to obtain mature eggs for fertilisation or vitrification.

In comparison with the traditional trigger of human chorionic gonadotrophin, GnRH agonist is associated with a much lower risk of ovarian hyperstimulation syndrome, making this a safer option for patients who need to get on with their cancer treatment.

## EMBRYO CRYOPRESERVATION VS OOCYTE VITRIFICATION

The most established technique to preserve fertility in women is embryo cryopreservation, but this of course requires the presence of a male partner. Future use of embryos requires both partners to consent to their use at that time, and hence careful counselling is required before choosing this option.

In recent years, the development of oocyte vitrification as a viable laboratory technique now allows women to store their unfertilised eggs and obviates the need for a male partner or future consent. Live birth rates from vitrified-warmed eggs are comparable with those from 'fresh' eggs, though the data are mainly from egg donors rather than cancer patients.

## PREPUBERTAL OPTIONS

Fertility preservation options for prepubertal girls and boys are still relatively less developed, but progress has been made in ovarian tissue cryopreservation. It is sensible to consider this still as an experimental treatment that requires a licensed laboratory and should be delivered in a research setting. The hope is that this will become a viable option for prepubertal girls and also for older girls and women where even the short delay for ovarian stimulation is contraindicated.

Stored ovarian tissue can be transplanted into the ovarian fossa ('orthotopic') or elsewhere ('heterotopic'). Orthotopic transplantation keeps open the possibility of natural conception.

## MEN AND BOYS

I have not discussed here the options available for men and boys needing to preserve their fertility. However, the general principles of need and appropriateness apply equally to them. Sperm cryopreservation is an established and successful method and widely available in the NHS. In contrast, options for prepubertal boys are experimental, although exciting laboratory work is occurring in *in vitro* spermatogenesis, using frozen-thawed testicular tissue.

Like other fast-moving and complex areas, fertility preservation requires clinicians to be aware of their options and local pathways, so that they can offer their patient the best advice. For interested colleagues, the British Fertility Society has set up a Fertility Preservation Special Interest Group ([www.britishfertilitysociety.org.uk/special-interest-groups/fertility-preservation-uk](http://www.britishfertilitysociety.org.uk/special-interest-groups/fertility-preservation-uk)) and has also published peer-reviewed guidelines dealing with these issues.<sup>1</sup>

## RAJ MATHUR

Consultant Gynaecologist and Subspecialist in Reproductive Medicine and Surgery, Manchester University NHS Foundation Trust

## REFERENCE

1. Yasmin E *et al.* 2018 *Human Fertility* **21** 3–26.



# KISSPEPTIN: THE MASTER REGULATOR OF REPRODUCTION?

WRITTEN BY ALEXANDER N COMNINOS & WALJIT S DHILLO



Back in 1996, a research team led by Danny Welch at the University of Pennsylvania (Hershey, PA, USA) first identified the kisspeptin gene (*KISS1*) for its anti-metastatic properties in malignant melanoma.<sup>1</sup> Little did they know that, over 20 years later, kisspeptin would be positioning for the role of master regulator of reproduction.

They named it after the most famous local product from their university campus town in Hershey: the chocolates called 'Hershey's Kisses' (Figures 1 and 2). It seems therefore somewhat appropriate that kisspeptin, containing as it does the word 'kiss', would several years later emerge as a key hormone in reproduction.



**Figure 1.** Hershey's Kisses, the chocolates that gave their name to kisspeptin. ©A Comninios and W S Dhillon



**Figure 2.** A visit to the Hershey's chocolate factory in Pennsylvania. ©A Comninios and W S Dhillon

## REVEALING KISSPEPTIN'S ROLE

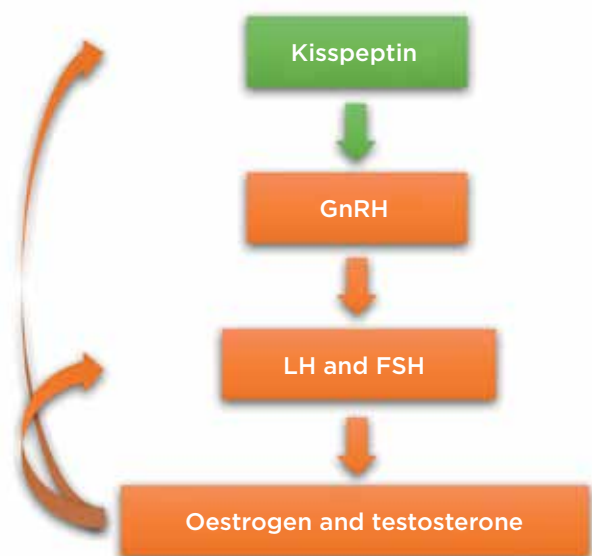
It was in 2003, 7 years after the initial discovery of kisspeptin, that its crucial roles in reproduction began to emerge. Two large consanguineous families (from France and Saudi Arabia) had sought medical review for infertility. Five of the eight children in the French family and six of the nineteen children in the Saudi Arabian family were diagnosed with infertility due to hypogonadotrophic hypogonadism.<sup>2,3</sup>

Mutation analyses revealed inactivating mutations in the kisspeptin receptor gene. Subsequent studies demonstrated that inactivating mutations in the kisspeptin gene itself also resulted in hypogonadotrophic hypogonadism,<sup>4</sup> while, conversely, activating mutations resulted in central precocious puberty.<sup>5</sup> Hence, the stage was set for an explosion of interest in exploring the roles of kisspeptin in reproduction.

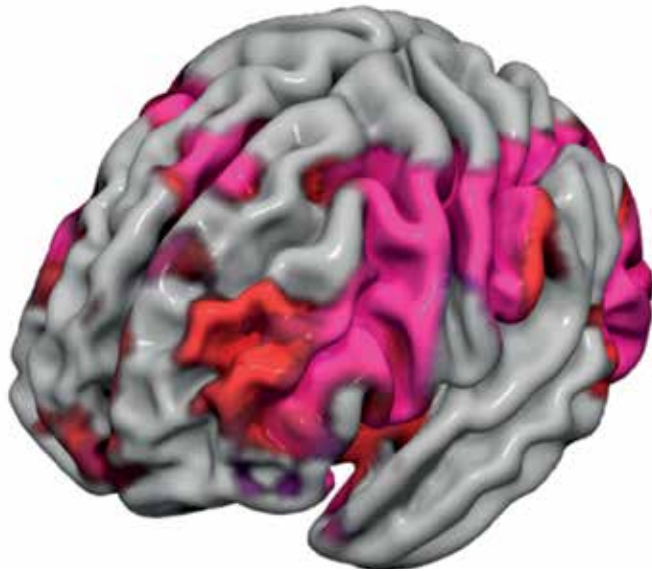
## THE APEX OF THE AXIS

It soon emerged that kisspeptin is positioned at the apex of the reproductive axis (Figure 3). Kisspeptin is secreted by specialised kisspeptin neurones within the hypothalamus. It activates kisspeptin receptors upon gonadotrophin-releasing hormone (GnRH) neurones, resulting in downstream stimulation of reproductive hormone release (luteinising hormone, follicle-stimulating hormone, testosterone and oestradiol). This ability of kisspeptin to stimulate downstream reproductive hormones was demonstrated in man in 2005 by the first kisspeptin into human study.<sup>6</sup>

The ability of kisspeptin to regulate reproductive hormones was studied in earnest over the next decade in a variety of species (from zebrafish to humans).<sup>7,8</sup> These studies revealed that kisspeptin neurones integrated with a variety of other hormones and neuropeptides, including prolactin,



**Figure 3.** Kisspeptin sits at the apex of the reproductive axis (GnRH, gonadotrophin-releasing hormone; LH, luteinising hormone; FSH, follicle-stimulating hormone). ©A Comninios and W S Dhillon



**Figure 4.** Kisspeptin enhances sexual and emotional brain processing.  
©A Comninou and W S Dhillon

leptin, pro-opiomelanocortin, neuropeptide Y, vasopressin, oxytocin, GABA ( $\gamma$ -amino-butyric acid), glutamate, nitric oxide, neurokinin B, dynorphin, serotonin and dopamine. This placed kisspeptin in the centre of a web, orchestrating the reproductive, metabolic and behavioural control of reproduction.

Indeed, the mechanism whereby hyperprolactinaemia shuts down the reproductive axis is now believed to occur via prolactin receptors on kisspeptin neurones.<sup>9,10</sup> Similarly, positive and negative gonadal feedback on GnRH neurones also occurs predominantly via kisspeptin neurones, as GnRH neurones themselves lack the oestrogen receptor- $\beta$  required for feedback. GnRH neurones also lack leptin receptors – the effects of leptin on reproduction are executed via kisspeptin neurones.<sup>11</sup> Further roles for kisspeptin in circadian reproductive systems, including puberty initiation, mid-cycle luteinising hormone surge and seasonal reproduction, were soon identified.

### A ROLE IN BEHAVIOUR

Interestingly, kisspeptin signalling also occurs in key behavioural (e.g. limbic) structures of the brain and can influence reproductive hormone release.<sup>12</sup> With this finding, we became particularly interested in how kisspeptin may modulate human behavioural processing encompassing sex and emotions.

Using functional magnetic resonance imaging and a range of psychometric methods, we found that kisspeptin could enhance human limbic brain activity specifically when men viewed sexually stimulating images as well as non-sexual images of couples bonding (Figure 4). Furthermore, kisspeptin's ability to enhance limbic brain activity correlated with reward metrics, improved mood and reduced sexual aversion.<sup>13</sup>

Our human data, combined with studies in animals,<sup>14–17</sup> therefore suggest that kisspeptin can also modulate sexual and emotional processing, thereby integrating these with reproduction, perhaps to ensure survival of the species, or at least contributing to an urge for sexual activity. This opens up the exciting possibility that kisspeptin-based therapies may help patients with psychosexual dysfunction.

### ROLES BEYOND THE BRAIN

Kisspeptin also has roles in reproductive tissues beyond the brain, with studies implicating kisspeptin signalling in ovarian and uterine function, embryo implantation and placentation, as well as in testicular and sperm function.<sup>18</sup> Therefore, kisspeptin modulates not only central reproductive effects, but also acts directly on reproductive organs.

### LOOKING TO THE FUTURE

Danny Welch and colleagues in 1996 surely had no idea that, two decades after identifying the kisspeptin gene for its anti-metastatic effects, kisspeptin would be the subject of such excitement in the field of reproduction. Nearly 2,000 papers have been published since then, collectively demonstrating the crucial and multi-faceted roles of kisspeptin.

Indeed, last year, together with other kisspeptin researchers, we organised the 3rd World Kisspeptin Conference in Orlando (FL, USA), which was perhaps the equivalent of a 'Kisspeptin Disney World' such was the academic excitement experienced by all!

One particular area of excitement is how we can develop this basic, translational and clinical kisspeptin research into practice, for the benefit of our patients. In beginning to answer this, several studies have demonstrated that kisspeptin-based therapies may have a role in idiopathic hypogonadotropic hypogonadism, hypothalamic amenorrhoea, hyperprolactinaemia, *in vitro* fertilisation, polycystic ovarian syndrome and psychosexual disorders.<sup>10,13,19,20</sup> Translating these possibilities into routine clinical use will be the challenge for the next decade of kisspeptinology.

So is kisspeptin, indeed, the master regulator of reproduction? Certainly, its newly identified roles in reproductive hormone and organ control, feedback mechanisms and integration with metabolism, as well as in sexual and emotional behaviours, would suggest it may indeed be precisely that.

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# PLASTICS, PILLS AND PAINKILLERS: ENDOCRINE DISRUPTION AND MALE REPRODUCTIVE HEALTH

WRITTEN BY ROD MITCHELL



The impact of *in utero* environmental exposure on the future health of offspring is now an established concept in both science and society. We are bombarded with information about how the environment may affect our long term health. However, unpicking the evidence from a wealth of different chemicals and experimental designs to form definitive conclusions about the possible impact on humans is complex.

'Endocrine disruption' is often used to refer to the effects of such environmental exposures. However, whilst there may be many mechanisms by which these agents could impact physiological function, the term 'endocrine disruption' should be reserved for those that directly effect hormone production or action.

One of the first areas in which endocrine disruption was related to the impact of environmental exposures was male reproductive health. This remains the most commonly researched field, based largely on rodent studies.

1950s advertisement for the synthetic oestrogen DES.

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Historically, investigations have examined the anti-androgenic or pro-oestrogenic effects of industrial chemicals, such as those found in plastics. More recently, there has been an expansion of scientific literature on the effects of pharmaceutical exposure during pregnancy. In many ways, focusing our attention on pharmaceuticals seems a logical step, when we consider that therapeutic use of pharmaceuticals may result in regular exposure to relatively high concentrations of a drug. Here, I will focus primarily on the impact of pharmaceutical use during pregnancy on the male reproductive health of the offspring.

## WHERE HAVE WE COME FROM?

In the 1950s, diethylstilboestrol (DES), a synthetic oestrogen, was first used as a therapy for preventing miscarriage and preterm birth. It was widely promoted to pregnant women. However, by the end of that decade it had become apparent that exposure was associated with the development of vaginal malignancy in a small number of female offspring. Furthermore, a weak association with some male reproductive disorders, linked to a reduction in fetal testosterone production, was described. As a result of these findings, DES was withdrawn from clinical use.

Interestingly, despite evidence from rodent studies to support the association between DES exposure and reduced testosterone production by the fetal testis, no effect was demonstrated in studies involving human fetal testis exposed to DES, highlighting the importance of validating the results of rodent and epidemiological studies in experimental models that utilise human tissues.<sup>1</sup>

Over the next few decades, a limited number of studies reported the effects of pharmaceuticals on male reproduction. However, from the late 1990s, attention turned to the potential for analgesics to affect male reproductive health. Several epidemiological studies described an association between *in utero* exposure to analgesics and the development of male reproductive disorders (including testicular maldescent and hypospadias) in males born to exposed mothers.<sup>2</sup> Experimental evidence has subsequently demonstrated effects of exposure to analgesics on the human fetal testis.<sup>3</sup>

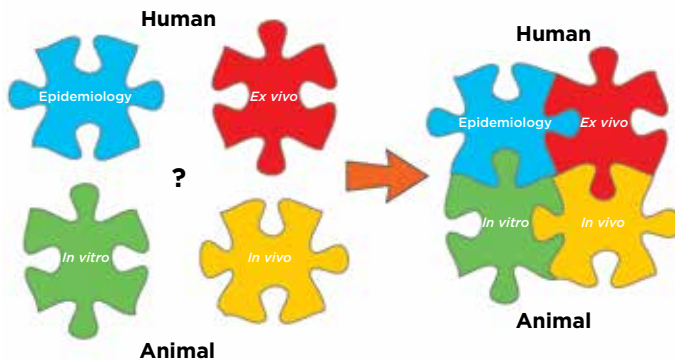
## WHERE ARE WE NOW?

Recently, experimental systems have been developed that utilise human fetal tissues. These have resulted in a number of publications investigating the effects of human-relevant dose and duration exposures using *in vitro* or xenograft approaches.

The recent development of a xenograft model to investigate the effects of exposure to proposed endocrine-disrupting chemicals has provided an *ex vivo* system in which to model human-relevant exposures over a more prolonged period than can be achieved with tissue culture *in vitro*, in a physiological system that aims to mimic human pregnancy. This involves administration of therapeutic regimens of analgesics to rodents carrying xenografted human fetal testis tissues.

These studies have demonstrated that paracetamol can reduce testosterone from the human fetal testis.<sup>4</sup> Furthermore, exposure to paracetamol or ibuprofen has also been shown to reduce germ cell number in human fetal testis and ovary.<sup>5</sup>

Importantly, whilst the effects on testosterone production can be considered as 'endocrine disruption', the analgesic effects on germ cells appear to be mediated by modulation of prostaglandin signalling.<sup>5</sup> This highlights the fact that, although an agent may be labelled as an endocrine-disrupting chemical, it may also lead to effects that arise through non-endocrine disrupting mechanisms.



It is necessary to combine knowledge gained from epidemiological studies with experimental approaches using rodent models and human tissues. ©R Mitchell

### WHERE DO WE GO FROM HERE?

So what is the current message regarding the use of analgesics in pregnancy? Overall, current evidence suggests that *in utero* exposure to therapeutic doses of analgesics (including paracetamol and ibuprofen) may result in negative effects on testosterone production in males and on germ cells in the male and female gonad.

However, given the limitations with human research, we still do not know what the long term impact of analgesic exposure during pregnancy might be on subsequent reproductive health and fertility. It is also important to remember that controlling pain and fever is important for the health of the mother and baby. Therefore, a pragmatic approach should be adopted in line with existing guidance.

Medications such as ibuprofen are already contraindicated in the first trimester and from 30 weeks of gestation, due to the risks of miscarriage and fetal cardiac abnormalities respectively. In the case of paracetamol, it should be used at the lowest effective dose for the shortest possible duration, and only where deemed necessary.

What has become clear from research into endocrine-disrupting chemicals is that, in order to assess the impact of proposed endocrine disruptors, it is necessary to combine knowledge gained from epidemiological studies with experimental approaches using rodent models and human tissues.

Whilst each approach provides valuable information, none of these approaches should be considered in isolation. Epidemiological studies demonstrating association must be confirmed in experimental models to determine the mechanism and should be further confirmed using human-relevant experimental systems. Care must be taken to ensure that epidemiological studies are rigorously conducted, ideally involving prospective design in order to assess accurately pharmaceutical use during pregnancy: not an easy task! Experimental models need to reflect how human exposure occurs in terms of route, dose, duration and mechanism of action.

Clinical advice and regulation of the use of environmental agents and pharmaceuticals during pregnancy is dependent on high quality scientific evidence. Collaborative work to combine the epidemiological and experimental evidence, and the refinement of human-relevant models that will permit new understanding of how the environment impacts on testicular development and function, may be key steps in achieving this goal.

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## OBESITY IN PREGNANCY: IS THE NEXT GENERATION AT INCREASED RISK?

WRITTEN BY HEATHER L BLACKMORE



Congratulations, you're pregnant! You may now think that it is time to 'ditch the diet' and start eating for two. In fact, guidelines from the National Institute for Health and Care Excellence (NICE) recommend only a 200-calorie increase, in the final 3 months of pregnancy.

In addition to the promotion of healthy gestational weight gain, rising levels of obesity worldwide are increasing the pressure to emphasise the importance of entering pregnancy at a healthy weight. Maintaining a

healthy diet and weight gain during pregnancy is vital in reducing the immediate adverse consequences to mother and child.

However, there is also evidence to suggest that exposure to obesity in pregnancy can increase a child's risk of non-communicable disease in adulthood.

### DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

Awareness of the concept that your environment *in utero* and early postnatal life is important for future disease risk came about from observational studies that showed a positive association between geographical areas of high neonatal mortality and ischaemic heart disease in adulthood. It was

postulated that this link could be attributed to the poor health of the mother in pregnancy and reduced fetal growth.<sup>1</sup>

Subsequent studies further investigated and supported these associations using low birth weight as a *proxy* marker of a poor intrauterine environment.<sup>2</sup> As birth weight is only an indirect indicator of maternal and/or fetal health, specific exposures have been investigated which include maternal undernutrition during periods of famine, glucocorticoid exposure due to premature birth and, most recently, maternal over-nutrition and obesity.

### FROM UNDERNUTRITION TO OBESITY

Obesity in pregnancy is associated with a plethora of complications in the mother that may include gestational diabetes, pre-eclampsia, inflammation and elevated lipid profiles. It is hypothesised that such an unfavourable environment can alter the molecular, structural and functional phenotype in the developing fetus, resulting in long-lasting changes that increase their risk of later adulthood disease.

A number of human studies have investigated the long term impact of exposure to maternal obesity. An Aberdeen cohort showed that offspring of obese mothers were more likely to die prematurely, and were at increased risk of hospital admission due to a cardiovascular event.<sup>3</sup> In two Finnish studies, one showed a 35% increased risk of atrial fibrillation,<sup>4</sup> and the other showed the highest mortality rates from coronary heart disease in offspring whose mothers had a higher body mass index during pregnancy.<sup>5</sup>

While human studies are vital, the prevalence of maternal obesity in these populations is relatively low, considering these mothers were pregnant 50–60 years ago. Frighteningly, the full impact of the current obesity situation is yet to be fully understood. This is where the use of animals is critical in our understanding, as they not only allow us to model human obesity and the impact of certain diets, but also help address mechanistic insight and causality. Furthermore, due to their shorter lifespans, they allow the study of age-associated conditions.



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*‘Obesity in pregnancy is associated with a plethora of complications in the mother that may include gestational diabetes, pre-eclampsia, inflammation and elevated lipid profiles.’*

### TYPES OF ANIMAL MODEL

There are a considerable number of animal models in this field of research, ranging from large species that include sheep to the smaller and more common rodent models. These models act to induce environmental changes in the mother to mimic human obesity and/or a poor diet. However, the type of model varies according to the question posed by the research group.

Those interested in understanding the impact of maternal obesity often feed high fat/high sugar diets prior to conception and throughout pregnancy and lactation.<sup>6</sup> This method provides an animal with both an unhealthy diet and a metabolic phenotype similar to that of an obese mother, such that they have raised body weight and fat mass, elevated lipids and insulin resistance.<sup>7</sup> Others may wish just to look at the effect of certain diets during pregnancy, or perhaps address the influence a particular diet has on the offspring during certain developmental windows of pregnancy and/or lactation.

The laboratory where I am based utilises a mouse model of maternal diet-induced obesity. The mice become obese through the consumption of sweetened condensed milk and a high fat diet pellet. These females are heavier, fatter and more insulin-resistant.<sup>7</sup> A causal link between offspring exposure to maternal obesity and cardiovascular disease has been consistently shown. Offspring of obese mothers have enlarged hearts from weaning, develop pathological left ventricular hypertrophy by 8 weeks of age and have impaired cardiac dysfunction coupled with enhanced activation of sympathetic tone.<sup>8,9</sup>

The long term goal of using animal models is to be able to uncover mechanistic insights into what it is about the maternal environment that is driving the offspring phenotype. These findings can then be translated back into humans, with the hope of targeted intervention strategies focused on either the mother or the offspring.

Intervention studies in humans and animals are already underway, acting through dietary modification, exercise or pharmacology, in the hope of reducing the offspring’s risk of cardiovascular disease, and improving the health of the mother both during and after pregnancy.

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# INDUCTION OF SPERMATOGENESIS IN MEN WITH GONADOTROPHIN DEFICIENCY

WRITTEN BY CHANNA JAYASENA, DU SOON SWEE, ANDREW DWYER & RICHARD QUINTON

Infertility affects approximately 15% of couples, and male factors contribute to roughly half of cases. Advances in assisted reproductive technologies (ARTs) now provide men with primary (testicular) infertility with treatment options. Notably, secondary infertility is one of the few forms of infertility that can be treated hormonally. This brief overview examines the induction of spermatogenesis in men with gonadotrophin deficiency.

Sperm development requires the co-ordinated endocrine action of follicle-stimulating hormone (FSH) and testosterone. FSH is crucial for seminiferous tubule development, inducing spermatogenesis in the testes and maintaining fertility. Luteinising hormone (LH) induces testosterone secretion from the interstitial Leydig cells.

Although testosterone circulates at nanomolar concentrations in the bloodstream, levels are 100-fold higher (i.e. micromolar) in the testes and testosterone acts in a paracrine manner to support spermatogenesis. Thus, men with secondary infertility (i.e. hypogonadotrophic hypogonadism) who lack adequate endogenous FSH/LH can receive hormone replacement to induce fertility. Importantly, exogenous testosterone will not adequately support spermatogenesis in men with gonadotrophin deficiency. Furthermore, in normal men, exogenous testosterone will inhibit spermatogenesis through suppression of endogenous LH and FSH secretion.

## PREDICTORS OF OUTCOME

Whereas females have already achieved their lifetime supply of oocytes before birth, males require three distinct phases of testicular maturation to develop and sustain spermatogenesis.

The first wave of testicular development begins *in utero*, with placental human chorionic gonadotrophin (hCG)-induced testosterone secretion (from 7 weeks of gestation). This is followed by gonadotrophin-releasing hormone-stimulated pituitary LH and FSH secretion during 'minipuberty' (during the first 4–6 months of life). It is completed in adolescence with the onset of puberty.

The minipuberty is a critical event for future fertility. This is a proliferative period and serum hormones reach near-adult levels. Notably, while erections may be noted on nappy changing, spermatogenesis does not occur at this point, as Sertoli cells do not express the androgen receptor until much later (around 5 years of age).

Males with absent minipuberty (i.e. in Kallmann syndrome or combined pituitary hormone deficiency) are characterised by 50% prevalence of maldescended testes (cryptorchidism), with or without micropenis, and

these patients typically do not have any subsequent spontaneous pubertal development in adolescence.

Several important predictors of outcome have been identified to date. Key factors adversely affecting fertility outcomes include smaller testicular volume (TV) and history of cryptorchidism. Gonadotrophin-deficient men with some spontaneous pubertal development (i.e. TV>4ml) respond better to gonadotrophin treatment and typically develop sperm within 6 months. Patients with severe gonadotrophin deficiency (i.e. TV<4ml and surgically corrected cryptorchidism) are less likely to ever develop sperm in the ejaculate.

## MONO- OR COMBINED GONADOTROPHIN THERAPY

Men with deficient LH and FSH secretion – hypogonadotrophic hypogonadism – have a hormonally treatable form of infertility. This, uniquely, can potentially be addressed solely in the endocrine clinic. However, it is good practice to engage with local fertility services at an early stage, in order to identify and address possible female partner subfertility, as well as to access ARTs as needed, if gonadotrophin therapy does not achieve optimal results (e.g. *in vitro* fertilisation (IVF), intracytoplasmic sperm injection (ICSI) or microdissection with testicular sperm extraction (micro-TESE)). Additionally, if treatment is successful, men may wish to cryopreserve sperm (by banking) prior to stopping gonadotrophin therapy.

Even prolonged hCG monotherapy rarely achieves useful spermatogenesis in men with congenital hypogonadotrophic hypogonadism (CHH), so it is pointless deferring FSH therapy until after an arbitrary period of puberty (e.g. following treatment of pituitary tumours) have a much better prognosis, and fertility can often be restored with hCG monotherapy. The very short half-life of recombinant LH precludes a clinically useful role in therapeutics. Hence, hCG is used to stimulate Leydig cells, with stable serum testosterone levels achievable through subcutaneous injection two or three times per week.

Should serum oestradiol begin to rise above the male range, the hCG dose will need to be reduced to mitigate the risk of developing gynaecomastia. Treatment should target normal serum testosterone levels in trough blood samples taken just prior to injection, while monitoring haemoglobin/haematocrit and possible gynaecomastia.

If monotherapy is unsuccessful, FSH can be added. It is available in 'pure' recombinant form, or isomolar with LH as human menopausal gonadotrophin, with either being suitable for spermatogenesis induction in males. Stable serum FSH levels are achievable through thrice-weekly subcutaneous injection (or new long-acting FSH analogue every 10–14 days).

Urinary-derived gonadotrophins are much cheaper than their recombinant counterparts. Unfortunately, supply for urinary-derived gonadotrophins is becoming ever more precarious, which threatens the provision of spermatogenesis induction in the NHS. It is really important to get more uniform access to these specialist medications that are so important to affected couples.



Predicting the success of spermatogenesis induction in male hypogonadotrophic hypogonadism.

Positive predictors	Negative predictors
<ul style="list-style-type: none"> <li>• TV<math>\geq</math>4ml, consistent with milder LH/FSH deficiency</li> <li>• Normally descended testes</li> <li>• Higher baseline serum inhibin B level (i.e. &gt;100pg/ml)</li> <li>• Spermatogenesis achieved in prior gonadotrophin treatment cycles</li> </ul>	<ul style="list-style-type: none"> <li>• Absent minipuberty</li> <li>• Absent spontaneous pubertal development (TV&lt;4ml)</li> <li>• History of maldescended testes (cryptorchidism) with surgical correction; late surgical correction (past first year of life)</li> <li>• Low baseline serum inhibin B (&lt;60pg/ml)</li> <li>• Mutation in <i>ANOS1</i> (formerly <i>KAL1</i>), an X-linked form of Kallmann syndrome</li> </ul>

Approximately 75% (CI 69–81%) of men with hypogonadotrophic hypogonadism will develop sperm in their ejaculate following mono- or combined gonadotrophin therapy. However, men with smaller TV (<4ml) do not have the same outcomes and their treatment requires a different approach.

### SEQUENTIAL GONADOTROPHIN THERAPY

For men with severe LH/FSH deficiency, combined gonadotrophin treatment has been the traditional approach to fertility induction. More recently, a sequential approach has been used in gonadotrophin-deficient men to recreate the events of early puberty and maximise fertility potential.

In this approach, FSH 'priming' is achieved by FSH monotherapy for 2–4 months. This recapitulates the rise in FSH early in puberty that is critical for proliferation of Sertoli and germ cells. The addition of hCG induces testosterone secretion and Sertoli cell maturation.

Initial reports show promising results even for those men with prepubertal testes and cryptorchidism (i.e. negative predictors of outcome). However, a large international multicentre trial is needed to definitively determine the optimal treatment (i.e. combined versus sequential gonadotrophin treatment) for the most severely affected men.

In summary, men with hypogonadotrophic hypogonadism have a treatable form of infertility. The majority of men can produce sperm in the ejaculate with appropriate, tailored treatment based on predictors of outcome. It is worthwhile noting that many men will not achieve normal sperm counts by the World Health Organization standard, yet low sperm count does not preclude fertility in these men. Such patients should be appropriately counselled on fertility chances and be monitored by endocrinologists who are experienced in using gonadotrophin regimens.

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## A PREGNANCY AUDIT FOR WOMEN WITH TURNER SYNDROME AND CAH

WRITTEN BY GERARD CONWAY



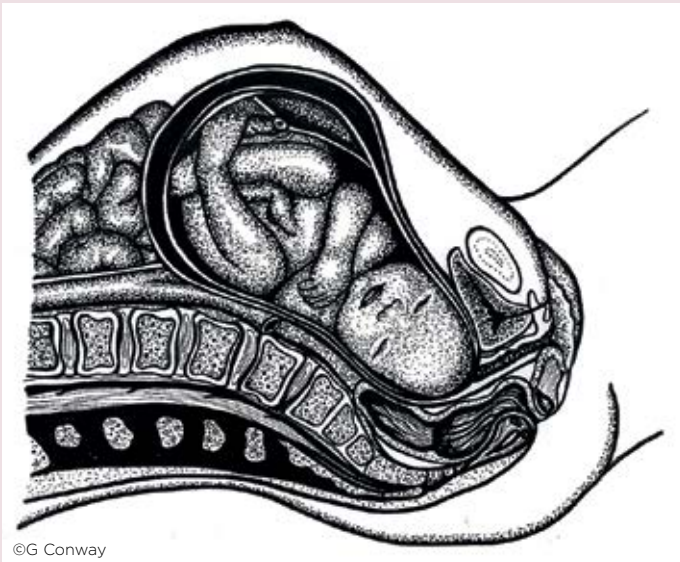
I write from Western Australia, having taken leave to travel the Gibb River Road to Darwin in Australia's Northern Territory. This long-held ambition is proving to be both a challenge and rewarding ... and a long way from University College London (UCL)!

I have briefly left behind one of the most exciting research projects of my career, in the capable hands of Antoinette Pimblett, Elizabeth Burt, Clementina La Rosa and Sasha Nair. The Reproductive Life Course

Project (RLCP) started in 2015, with the aim of collecting medical outcomes and life experiences from individuals with a variety of rare endocrine conditions such as Turner syndrome (TS) and congenital adrenal hyperplasia (CAH). The current focus of this research is to document pregnancy outcomes in women with these two conditions. We have been greatly assisted by two support groups: the Turner Syndrome Support Society and Living with CAH. In addition, the International Fund for CAH has financed the CAH component.

### A NEED FOR DATA IN TS

For over 20 years, my colleague Melanie Davies, with whom I have run the Adult Turner Clinic, has promoted the need for UK data on pregnancy in



©G Conway

TS. This need has grown all the more urgent as controversy has arisen over the magnitude of the risk of aortic rupture in this situation.

For most women with TS, the only way to achieve a pregnancy is by egg donation and *in vitro* fertilisation. Studies have shown that the risk of aortic dissection in pregnancy for women with TS after egg donation varies between 0.5 and 2%, but the series are very heterogeneous and modern adult care for women with TS was not yet established in most instances. It is also known that women with TS are prone to hypertension and pre-eclampsia in pregnancy, as well as premature delivery and low birthweight babies.

We now hope that a wide collaboration across the UK will build the world's biggest data set from women with TS who have ever been pregnant. In this way, we hope that these risks can be stratified to better inform future mothers-to-be.

#### ISSUES IN CAH

For women with CAH considering pregnancy, the issues are slightly different but equally important. Current knowledge of the experience of pregnancy for women with CAH is limited, as it has only been recently that fertility can be fairly easily achieved. One of the largest series reported the outcome of pregnancy in only 19 women.

*'We now hope that a wide collaboration across the UK will build the world's biggest data set from women with TS who have ever been pregnant. In this way, we hope that these risks can be stratified to inform future mothers-to-be.'*

*'There is much to learn about the safety of, and health in, pregnancy for women with a variety of endocrine conditions. We are starting with TS and CAH, but hope to expand to other conditions once the research network has become established.'*

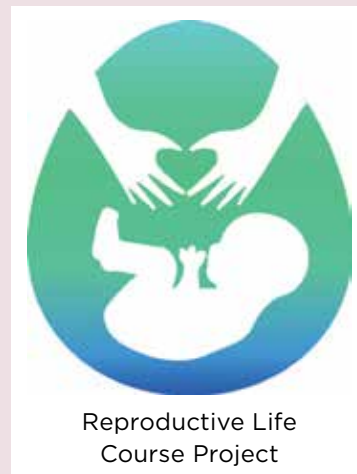
Taking the sparse literature as a whole, it seems as though there is an increased risk of gestational diabetes and premature delivery. Particular to CAH is the fact that most women with the severe forms have had vaginal surgery, and the risk of childbirth in this situation is a concern. We know that over 80% of women with CAH have a caesarean section. Anecdotally, it appears that some of those who have had vaginal delivery have not fared well, requiring post-operative corrective surgery. Lastly, in common with women with Addison's disease and hypopituitarism, women with CAH require stress doses of steroid cover during delivery, but guidelines for this lack a good evidence base.

#### A GREAT DEAL TO LEARN

In summary, there is much to learn about the safety of, and health in, pregnancy for women with a variety of endocrine conditions. We are starting with TS and CAH, but hope to expand to other conditions once the research network has become established. The process of data gathering entails a simple 30-minute telephone interview, currently undertaken by Drs Burt, La Rosa and Nair at UCL. Data could also be collected locally, as a great project for a new specialist registrar.

The task force for this project comprised Antonia Brooke, Melanie Davies, Helena Gleeson, Helen Simpson and Helen Turner. We have had a great response to an initial call for multicentre collaborators, and the doors are open for more. So far Barts, Birmingham, Brighton, Bristol, Cambridge, Exeter, Leeds, Newcastle, Oxford and Southampton have all completed or are in the process of R&D approval.

Our research co-ordinator is Antoinette Pimblett ([a.pimblett@nhs.net](mailto:a.pimblett@nhs.net)) and you can find out more at [www.rlep.uk](http://www.rlep.uk). Do get in touch!



Reproductive Life  
Course Project

With apologies to my team, I close with the unhelpful information that the Indian Ocean at sunset is a great place to be writing from, compared with Euston Road in a rainy rush hour! We are about to turn inland to go off grid for some weeks, but I look forward to catching up with progress on my return.

**GERARD CONWAY**  
Professor of Reproductive  
Endocrinology,  
University College London



## SPOTLIGHT ON MENOPAUSE

WRITTEN BY ANNICE MUKHERJEE

Improved information provision for women going through menopause is essential to enable them to make informed choices about management and maintain health and well-being through the climacteric period.

The average age of onset of menopause is 51 years, but there is significant variation. Approximately 1% of women experience menopause before the age of 40 years, this is described as premature ovarian insufficiency (POI). High-dose alkylating agents and ovarian radiotherapy are associated with POI and the overall prevalence of POI in childhood cancer survivors was found to be 10.9% in a recent publication.<sup>1</sup>

### ONSET AND SYMPTOMS

Approximately 70% of women will suffer with symptoms. These may occur before menopause is biochemically evident. In most women, symptoms spontaneously improve over 4–8 years. The majority of women do not seek medical intervention and, of those who do, many will require only information and advice. However, around 25% have problematic symptoms that may need treatment.

Vasomotor symptoms are the main reason that women seek help. A variety of other problems can, however, be quite distressing, including sleep disturbance, mood changes, fatigue, joint pains, sexual dysfunction, urogenital symptoms and skin and body habitus changes, among other issues.

Our primary care colleagues will do their best to manage patients with milder symptoms. However, there is likely to be a steady stream of women suffering severe symptoms, and those with more complex medical backgrounds, including cancer survivors and women with POI, who require more specialised guidance on management. So this is a topic we all need to know about!

### RECENT MEDIA INTEREST

In recent years, the press has given ever-increasing publicity to this topic. In November 2015, the National Institute for Health and Care Excellence (NICE) guidance on menopause and its management was published.<sup>2</sup> The European Society of Human Reproduction and Embryology (ESHRE) published a guideline on management of POI in the same month,<sup>3</sup> focusing on the unique management needs of this cohort. Collaborative recommendations for POI surveillance for female survivors of childhood, adolescent and young adult cancer were published in 2016.<sup>4</sup>

The NICE guidance received considerable interest in the general media. In particular, a multitude of media reports suggested that menopausal women were experiencing workplace discrimination. There were 3.5 million women aged 50–65 in employment in the UK in 2013. An estimated 10% of women had taken days off work because of menopausal symptoms, but only one in four had discussed their symptoms with their line manager.

The Chief Medical Officer (CMO), Professor Dame Sally Davies published a press release in December 2015, which called on employers to create a culture where women feel comfortable discussing menopause in the workplace. At the request of the CMO, the Faculty of Occupational Medicine (FOM) produced guidance on menopause and the workplace in 2016.<sup>5</sup> The guidance was featured in a documentary for ITV's *Tonight* programme: 'The Truth about the Menopause'.

More recent social media interest has included the Society for Endocrinology's Public Engagement Committee Chair, Maralyn Druce,

who was interviewed in 2018 by Manuela Saragosa on a BBC Business daily podcast about oestrogen and the menopause.<sup>6</sup>

These public engagement exercises are most welcomed by the public, who may receive conflicting information from the lay press about menopause and its treatment.

### MANAGEMENT OPTIONS

Following on from the initial results of the Women's Health Initiative (WHI) published in 2002<sup>7</sup> and the Million Women Study publication in 2003,<sup>8</sup> use of hormone therapy took a sharp downturn, because overall health risks were thought to exceed benefits for all women. However, subsequent subgroup analysis from the WHI and many other studies have clearly shown that younger women and those close to menopause have a beneficial risk-to-benefit ratio.

In younger women treated with hormone therapy, the number of cases of venous thrombosis and ischaemic stroke was low. Breast cancer rates were also low and were found to be decreased with oestrogen therapy alone. Long term benefits of oestrogen therapy on bone health are undisputed.

Studies of risks linked with duration of treatments, dose and route of delivery, use of micronised progesterone (rather than synthetic progestogens) for endometrial protection in women with an intact uterus, and the use of oestrogen alone in hysterectomised women, have demonstrated that risk stratification can be applied to minimise previously documented cardiovascular, thromboembolic and breast cancer risks and also to identify those unsuitable for hormone therapy.

It has been argued that, since WHI, many women have been denied hormone therapy, including those with severe symptoms, and that this may have significantly disadvantaged a generation of women.

A significant proportion of women are unable to use hormone therapy due to risk factors and comorbidities. A number of non-hormone pharmacological therapies and natural approaches are available that women often find useful.<sup>9</sup>

For women suffering severe menopausal symptoms an individualised, tailored approach to management is critical for a successful outcome.

### ANNICE MUKHERJEE

Clinical Committee Representative, and Consultant Endocrinologist and Honorary Senior Lecturer, Salford Royal Hospital NHS Foundation Trust, Northern Care Alliance NHS Group

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# TESTOSTERONE TREATMENT AND CARDIOVASCULAR RISK: AN UNANSWERED QUESTION

WRITTEN BY AGNIESZKA SWIECICKA



Over the past two decades, we have seen an increase in testosterone prescribing worldwide. This is partly driven by increased awareness and identification of hypogonadism, but inappropriate use of testosterone in men without a clear antecedent diagnosis of hypogonadism has also contributed significantly to this phenomenon.

Several studies of testosterone replacement therapy (TRT) in men with so-called 'classic' primary or secondary hypogonadism have clearly demonstrated positive effects of testosterone replacement on body composition, muscle mass, bone mineral density and sexual function. However, significant concerns have been raised in more recent years over the potential cardiovascular (CV) risks associated with testosterone use, particularly in older men. Whilst data from retrospective epidemiological studies are largely conflicting, adequately powered randomised controlled trials to assess the long-term CV risks of TRT in men with low testosterone are simply lacking.

## IDENTIFYING A RISK

The potentially heightened CV risk among some groups of men treated with testosterone first came to light in 2010. A randomised trial of testosterone therapy in older men with low testosterone (3.5–12.1 nmol/l), impaired mobility and high co-morbidity burden (the Testosterone in Older Men with Sarcopenia (TOM) trial) was prematurely terminated, due to the higher frequency of CV-related adverse events in the testosterone-treated men compared with the placebo arm.<sup>1</sup> The participants were, however, prescribed rather large doses of testosterone, and the risk of a CV event was greatest in men with testosterone levels in the highest quartile during the intervention period, as compared with all other subjects.

*'Significant concerns have been raised in more recent years over the potential cardiovascular risks associated with testosterone use, particularly in older men.'*<sup>2</sup>

Subsequently, Vigen and colleagues reported an association of TRT with increased risk of myocardial infarction (MI), stroke and all-cause mortality in a cohort of 8,709 men aged 60–64 years with low serum testosterone (<10.4 nmol/l) who had undergone coronary angiography (hazard ratio 1.29; 95% CI 1.05–1.58).<sup>2</sup> However, the study output was significantly influenced by the large number of questionable adjustments made to the analysis. The unadjusted analysis suggested that the rate of CV events was quite the opposite of what the study concluded: only 10.1% of men in the testosterone-treated group, as opposed to 21.2% in the untreated group, had a CV event.

Similarly, Finkle *et al.*, after examining the electronic records of 55,539 men who were prescribed testosterone, reported an increased relative risk of acute MI within 90 days of starting TRT compared with the rate of MI the year before (rate ratio 1.36; 95% CI 1.03–1.81).<sup>3</sup> However, the absolute risk of developing acute MI following TRT initiation was very low, accounting for an additional 1.25 cases per 1,000 patient-years. Moreover,

no information was provided regarding indications for testosterone treatment, including pretreatment testosterone level and presence of relevant symptoms. Therefore, it is unclear whether the treated men were indeed hypogonadal.

The studies by Vigen and Finkle have since received a significant amount of criticism, predominantly for their flawed design and methodology, as well as the reliability of the data presented and their interpretation.

## EVIDENCE TO THE CONTRARY

Contrary to these studies, Shores and colleagues showed that TRT in men with low testosterone, including those with pre-existing ischaemic heart disease, was associated with reduced all-cause mortality compared with the untreated men (hazard ratio 0.61; 95% CI 0.42–0.88).<sup>4</sup>

Similarly, a number of meta-analyses investigating the association between TRT and major adverse cardiovascular events (MACE) and mortality in randomised controlled trials and observational studies showed no clear association between CV risk and testosterone use.<sup>5,6</sup> The authors did, however, point out a significant clinical and methodological heterogeneity amongst the studies included in the meta-analyses, namely varied eligibility criteria, testosterone dosing and formulations, intervention duration, lack of large trial cohorts and a sufficient number of MACE. They concluded that, therefore, the overall evidence is rather limited and precludes a definitive conclusion regarding the adverse cardiovascular effects of testosterone.

## IN PRACTICE

In response to mounting concerns, and based on available data, the US Food and Drug Administration issued a statement concluding that, despite conflicting evidence, there is a possibility of increased CV risk associated with testosterone use. Testosterone manufacturers were instructed to add information regarding a possible increased risk of MI and stroke in testosterone users to their labelling. The European Medicines Agency concluded that there is no consistent evidence of an increased risk of coronary heart disease associated with testosterone therapy in hypogonadal men.

Overall, the data on TRT and CV events are scant and of insufficient quality to draw definite conclusions on this important topic. An adequately powered randomised controlled trial is needed to address this specific concern. Until this is clarified, clinicians should offer testosterone treatment only to men with proven testosterone deficiency (i.e. consistently low morning serum testosterone and signs and symptoms of androgen deficiency) and be cautious in those with relevant co-morbidities.

## AGNIESZKA SWIECICKA

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## MENTORING, AND MENTEE: ON MENTORING...



WRITTEN BY OLLIE MINTON

I am not a fan of tick boxes, the e-portfolio or 'all that jazz': the need for countless sign-offs now seems to start after fresher's week and to continue till retirement. I am, however, a great believer in life-long learning, continuing professional development (CPD) and, dare I say it, teamwork.

Firms may have gone (hopefully temporarily), and shifts can destroy continuity. It can be hard to make (and keep) professional friends. While social media and the online world can fill some of these gaps for learning and CPD, they can't replace the nuance of a decent chat.

This is where mentoring comes in for me. I want to be able to informally give advice and encouragement outside the 'educational supervisor and tick box' world. However, to my mind, this is an ad hoc system and we are all busy. Consequently, I put myself forward to be a Royal College of Physicians mentor, and completed the necessary 2-day training course and all the homework and CPD points that came with it.

I did it at the end of last year, on 2 days which were 2 months apart. I was surprised by the range of specialties and the enthusiasm of the room. There was a large focus on regulating the relationship, which I had not thought was needed, and on drawing up agreements. Clearly being badged by the College added a layer of bureaucracy and regulation.

I can see there is a power relationship, as most mentors will be more senior clinicians – if not a consultant then certainly more experienced doctors. However, we are all professionals and something less formal ought to be more than sufficient, in my mind. However, the rules are there to protect all concerned, even if you don't feel you need to be.

The days focused on potential models of being a mentor. There was a stress on the differences from usual educational supervision. Equally, you are not meant to be a spiritual guide/counsellor/any sort of therapist or a short cut for those too lazy to Google.

*'I am a great believer in life-long learning, continuing professional development and, dare I say it, teamwork.'*

The models are very varied and not necessarily strictly evidence-based. The theoretical approaches are more based on educational theory than hard science, but all intuitively make sense.

The top tips which the RCP produced are as useful as any ([www.rcplondon.ac.uk/news/ten-tips-successful-mentoring](http://www.rcplondon.ac.uk/news/ten-tips-successful-mentoring)). GPs use the skilled helper model and anyone who has had any cognitive behavioural training or experience will recognise the use of Socratic questioning and SMART goals ([www.gp-training.net/training/communication\\_skills/mentoring/egan.htm](http://www.gp-training.net/training/communication_skills/mentoring/egan.htm)).

The College gives a very reasonable introduction at <https://rcp.onpld.com/learn-more> and, as it stands, the course is free as a member/fellow, and comes with 12 CPD points.

At this point, I feel I should confess that, despite my 2 days of training and being registered with the College website, I have yet to be approached by a single mentee. The reasons for this I am still yet to fathom; I am not taking it personally, plenty of others are in the same position. I think sadly that, during all the winter pressure chaos and rota gaps, the idea of mentoring was farcical to some.

I over-emphasise the point, as those who take even a short time to pursue mentoring will reap significant benefits, I have no doubt. This was a motivated group of consultants who wanted to help. What we cannot do is overturn the system, but we could perhaps encourage others not to reinvent the wheel and provide some objectivity. With no prior relationship or vested interest you can ask the 'innocent' questions and continue to be supportive for those too lazy to Google.

*'Those who take even a short time to pursue mentoring will reap significant benefits, I have no doubt.'*

I think, in conclusion, I would say for the points/lunch and the excuse to go to the College the course is worthwhile – and also for confirmation that no one has all the solutions! However, we are all also time-poor and I do not see that there is any reason not to run something locally with your educational department. The more of these courses you do, the more you see the underpinning theory is the same for most if not all of them. A flip-board, some facilitated discussion and catering should be all you need.

We should all want to be mentoring and coaching as much as possible. We all probably are already, and are just not calling it that. I don't think it needs to be made more formal, simply to encourage everyone to recognise its use and to appreciate it is not just about ticking a box and missing the point.

OLLIE MINTON

Macmillan Consultant in Palliative Medicine, Brighton and Sussex University Hospital





## MENTORING, AND MENTEE: ON BEING A MENTEE...



WRITTEN BY SAIRA HAMEED

A perennial highlight of this magazine is the series 'An interview with...' in which a giant of endocrinology is asked to reflect on their achievements and their career. One question that is invariably asked is 'Who were your mentors?' Each of these endocrinology greats will describe the enormous impact that their mentors had on them personally and professionally, often attributing many of the choices that they made to that mentor-mentee relationship.

These interviews vividly depict the way that this connection between mentor and mentee can be pivotal within the story of a career and the final path taken.

As a mentee, I have found that the changes in medical training have made this relationship even more vital. The loss of the firm-based apprenticeship model can engender a feeling of transience when training, the notion that you are not known by anyone in particular, because of the brevity of the contact and the rapid succession of placements.

*'In a world of assessments made using electronic tools and drop-down boxes, this personal investment from a mentor is profound and life-enhancing.'*

A mentor therefore serves as a constant over many years, irrespective of where you are currently working. This relationship is frequently not formalised, but grows because the mentor generously, within an already crowded life, gives their time and attention to a junior colleague. In a world of assessments made using electronic tools and drop-down boxes, this personal investment from a mentor is profound and life-enhancing.

The endocrine giants interviewed in *The Endocrinologist* often cite two or three mentors who have guided them over the decades, identifying where in their career a certain mentor had a very particular impact. This illustrates that there is no perfect mentor but that, for a mentee, timing and context are everything.

At certain career points, a mentee might identify someone whom they consider a better, more senior version of themselves and will look to the mentor for answers to the question 'How can I get to where you are now?' This is not about nepotism or jobs for the boys or girls, but about accessing 'know how' which the mentor has developed and refined over many years that is now generously shared with the mentee.

Other mentees will admire their mentor, but not aspire to that particular version of endocrine success. This relationship is therefore not about a road map, but draws on the aspects of the mentor's experience and acumen that are universally relevant to diverse career paths and choices. One of the great strengths of this type of mentor is that their wisdom

lives on in the mentee many years after the face-to-face contact ceases. This means that, when confronted with a career, research or clinical dilemma, a mentee will wonder 'What would X [*insert name of mentor*] do?' In considering this question, the answer to the problem declares itself.

Endocrinology is a broad church, comprising clinical work, research and teaching. Mentors are likely to have a particular strength in one of these areas – but locating all three in one individual mentor would be a rare find. This means that when choosing a mentor, we mentees have to be sure that we are asking the right things of the right people. For a rewarding relationship on both sides, the mentor and mentee must be speaking the same language.

Put simply, if you require clinical mentorship, seek out a clinician you admire. If you are looking for academic mentorship ask a researcher whose work or approach resonates with you. If it's teaching mentorship, speak to the best teacher that you have had the privilege to be taught by.

As with all relationships, the mentor-mentee relationship requires a connection on both sides. It's rare that there are 'bad' mentors or 'bad' mentees, and more probable that there is simply a lack of compatibility between the protagonists. For often intangible reasons, mentees will feel 'a click' with some potential mentors and not others, but endocrinology would be a dull place if we were all the same.

One common hitch in the relationship is when a mentor makes themselves, rather than the mentee, the focus of the relationship, trying to fit the mentee's questions or choices into their own narrative. A good analogy might be a situation where the mentee says that their vision has deteriorated and they plan to go to the optician, only for the mentor, in response, to whip off their own glasses and say, 'Give these a try, they have always worked brilliantly for me.'

*'When confronted with a career, research or clinical dilemma a mentee will wonder "What would X do?" In considering this question, the answer to the problem declares itself.'*

A career in endocrinology affords us a diverse and endlessly absorbing professional life. The vastness of the subject matter and the rich and varied opportunities available to endocrinologists require planning and navigation, and having guidance can be hugely beneficial. The word 'mentor' in fact is derived from the character Mentor, a trusted and experienced guide and advisor in Homer's *Odyssey*. Three millennia after Homer wrote his epic poem, mentors continue to play a deeply important role in the nurture, guidance and care of mentees, providing us with the maps and charts that allow us to navigate our own endocrine odyssey.

SAIRA HAMEED  
Consultant Endocrinologist, Imperial College Healthcare NHS Trust,  
London

## Laying foundations FOR THE FUTURE

In our last members' survey, you told us that more effort is needed to encourage the next generation of clinicians, scientists and nurses into endocrinology. Your call has not gone unheard, and many initiatives are taking shape to ensure our discipline moves into the future, fresh with new talent.

### ENLISTING ENDOCRINE AMBASSADORS

Endocrinology extends across many aspects of research: there is no such thing as a typical 'endocrine scientist'. It was in light of this that we launched our Endocrine Ambassador scheme for our scientist members, to encourage researchers to 'pick up the flag' and raise the profile of endocrinology amongst colleagues in medicine.

These Endocrine Ambassadors are poised to play an important role, **showcasing endocrinology's many different flavours** so that students and colleagues appreciate the breadth the discipline has to offer. To help them achieve this, the Society makes funding available for Endocrine Ambassadors to invite speakers to their institutions, opening the door to interdisciplinary collaborations for current researchers, and showing students where endocrinology may be able to take them.

Find out more about Endocrine Ambassadors at [www.endocrinology.org/membership/endocrine-ambassadors](http://www.endocrinology.org/membership/endocrine-ambassadors).



### BOOSTING ENDOCRINE NURSE NUMBERS

Endocrine nurses are an integral part of many clinical teams across the UK, with the specialism continuing to grow. A push to **increase the visibility of endocrinology** to young nurses is currently underway. Improving the information provided on the Society website is an important part of our strategy, as it acts as a portal, enabling new nurses to learn what our discipline has to offer.

Combining an online presence with a physical presence can be effective in reaching new audiences, so the Society attended the Royal College of Nursing's International Nursing Research Conference in May. With the help of our Nurse Committee members, this was a fantastic opportunity for nurses to hear first-hand an account of the life of an endocrine nurse, and the unique balance of chronic and acute medicine it offers.



**Anne Marland**  
Nurse Committee member  
(Oxford)



**Sherwin Criseno**  
Nurse Committee member  
(Birmingham)

### TASTER DAY TEMPTATION

Many trainee clinicians don't get the opportunity to experience what endocrinology has to offer. This sometimes leads to misconceptions about what the discipline involves. While specialist rotations offer the opportunity to remedy this problem by providing practical experience, initial interest needs to be generated if trainees are to enrol.

Trying to change perceptions is no easy task, especially not in a single day. Yet, as you may have seen in issue 126 of *The Endocrinologist* (Winter 2017), Early Career Steering Group members Louise Hunter and Shazia Hussain managed just that, with their successful diabetes and endocrinology taster day last year. Work is underway to replicate this success, with the aim of taking the format to different regions across the UK, utilising local clinicians to help address the low uptake that some areas suffer.

You can find out more about endocrine career pathways and Society training and career development opportunities at [www.endocrinology.org/careers](http://www.endocrinology.org/careers).



**Louise Hunter**  
Early Career Steering Group  
(Manchester)



**Shazia Hussain**  
Early Career Steering Group  
(London)

# A Big Bang in Birmingham!

## TIME FOR ENDOCRINE INSPIRATION

Each year, thousands of schoolchildren and families flock to the Birmingham NEC for The Big Bang Fair to learn about all things 'STEM' (science, technology, engineering and maths).

This year's event took place on 14–17 March 2018. Standing alongside other bioscience societies as part of the Biology Big Top (a public engagement collaboration of bioscience societies), Society members were on hand with vials of 'blood' to draw in the curious attendees and explain how hormones regulate blood sugar levels.

Student member Jasmine Johal took a break from writing her dissertation to participate in the event, and found the event very valuable: 'It's very different from anything I have ever done, but it was a really enjoyable experience.' While dealing with almost 2,000 children across 2 days sounds intimidating, volunteers drawn from the Society's membership handled the questioning crowds wonderfully. 'I feel that the public thought the idea of them changing the "patient's" blood glucose levels was exciting – so that is a really good concept,' commented Jasmine.

Playing the role of the pancreas, the children had to test the glucose levels of samples and return them to the normal range using glucagon or insulin solutions. In truth, the whole set up may merely have been water, food colouring and dextrose at varying dilutions, but the simple demonstration opened the door to understanding an important body function. With many of the children having relatives or classmates with diabetes, the real world relevance of the activity came to the fore.

*"I really enjoyed participating at the Big Bang Fair. I thought the activity was really good; children always like practical things to do. I'm always happy to volunteer again."*

*Lisa Shepherd, Chair, Nurse Committee*



Volunteers: Jasmine Johal, Lisa Shepherd and Lorna Gilligan (not pictured: Antonia Jurd, Angela Taylor). Society staff: Matt Grant.

Showcasing the interdisciplinary nature of the biosciences, long-standing collaborators and fellow Biology Big Top members were also involved. In addition to the blood glucose activity, the Biochemical Society came prepared with an activity focusing on gene editing, the British Pharmacological Society taught attendees how medicine is made, and the Genetics Society showcased the wonders of the human chromosome. With lots of interest in each activity, hopefully some of the children will have found the spark to cause a 'big bang' in the world of biology!

*"It was an enjoyable day and got really busy!"*

**Antonia Jurd, Society member**

## Do you have a great idea TO ENGAGE NON-SPECIALISTS WITH HORMONES AND THE IMPACT OF ENDOCRINOLOGY?

Apply for a Public Engagement Grant of up to £1,000 before 26 September 2018  
Visit [www.endocrinology.org/grants](http://www.endocrinology.org/grants) for more information.

Visit [www.endocrinology.org/outreach](http://www.endocrinology.org/outreach) for free guides and templates to help you plan and deliver your outreach activities more effectively.



# An interview with...

## COLIN FARQUHARSON

### NEW CO-EDITOR-IN-CHIEF OF TWO SOCIETY JOURNALS



Professor Colin Farquharson (Edinburgh) was recently appointed Co-Editor-in-Chief of two of the Society's journals: *Journal of Endocrinology* (JOE) and *Journal of Molecular Endocrinology* (JME). Based at the University

of Edinburgh-Roslin Institute, his research focuses on the fundamental cellular mechanisms underpinning bone and cartilage growth, development and function. We spoke to Professor Farquharson about his new appointment, his work with the Society and his research.

#### WHAT INSPIRED YOU TO GET INVOLVED IN ENDOCRINOLOGY AND BONE RESEARCH?

I was introduced to bone research during my PhD, back in the late 1980s, in Aberdeen, where I investigated the effects of copper deficiency on collagen in the skeleton and cardiovascular system. However, I was really inspired during my first postdoctoral position with Nigel Loveridge, who introduced me to the growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis, and its control of endochondral ossification and skeletal development. This interest has stayed with me throughout my career.

#### WHAT ARE YOUR CURRENT RESEARCH INTERESTS?

My main interest is the GH/IGF-1 axis and its effects on bone formation and endochondral growth, and how disease states such as chronic kidney disease, muscular dystrophy and inflammatory bowel disease affect bone development and turnover. The mechanisms of skeletal mineralisation and, in particular, the role of phosphatases are also an ongoing research interest.

I think there is potential to harness the power of the GH/IGF-1 axis to prevent growth retardation and bone loss in a variety of genetic and inflammatory diseases.

#### HOW DO YOU FEEL ABOUT YOUR NEW ROLE AS CO-EDITOR-IN-CHIEF OF JOE/JME?

I am excited by the ability to contribute to the success and direction of two journals that are established leaders in publishing basic endocrine research. Whilst this is a position of great responsibility, it is also a great opportunity to work with talented senior editors and a dedicated publishing team, who collaborate effectively to ensure the highest quality research is published in both journals.

#### WHAT WAS IT LIKE BEING A SOCIETY FOR ENDOCRINOLOGY ENDOCRINE NETWORK CONVENOR?

The Bone and Calcium Endocrine Network (BACN) provided a forum to bring like-minded basic and clinical researchers

together and encourage cross-disciplinary research. Specifically, the BACN enabled Society members with an interest in skeletal physiology and metabolic bone disease to come together, share research ideas and best clinical practice, and to find solutions to the challenges they face. It was a pleasure to work with Duncan Bassett as the first joint convenors of the BACN, to help make this happen.

#### WHAT ARE THE BIGGEST CHALLENGES IN YOUR RESEARCH FIELD RIGHT NOW?

In common with many other research fields, obtaining sufficient research funding to support our research ideas continues to be an enormous challenge. Many excellent grant applications (as observed through the peer review system) are not funded. Rather gloomily, this situation is unlikely to change in the near future.

#### WHAT DO YOU THINK WILL BE THE NEXT BIG BREAKTHROUGH IN YOUR FIELD?

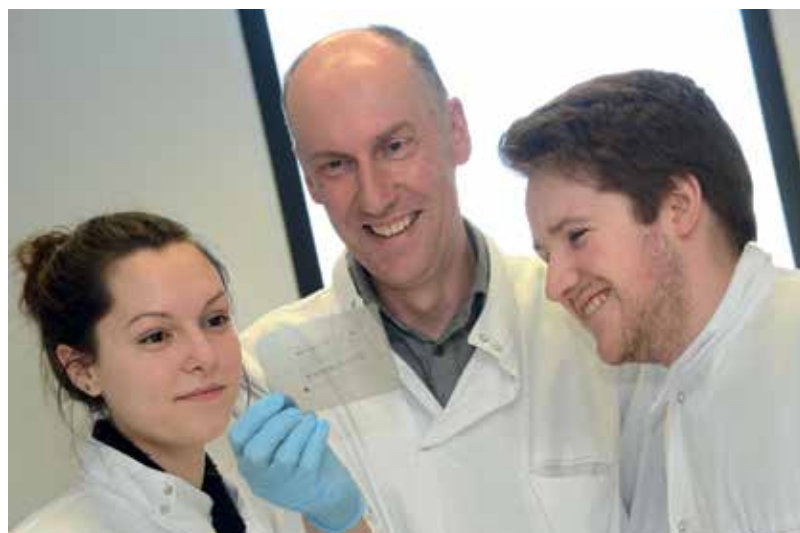
It's impossible to predict, but it is imperative and timely that regulatory mechanisms are defined and applied in new strategies to therapeutically control joint disease in osteoarthritis. Existing treatment programmes for osteoarthritis are extremely limited and centre on pain management. This lamentable situation is partly due to our incomplete understanding of the mechanisms by which cartilage and bone changes develop in osteoarthritis. I hope that ongoing and future scientific enquiry, which may involve an endocrine component, will help in this goal.

#### DO YOU HAVE WORDS OF WISDOM FOR ASPIRING ENDOCRINOLOGY RESEARCHERS?

Some of my proudest professional experiences have involved the opportunity to guide and advise young scientists and to see them develop into fully fledged independent research scientists. Two thoughts come to mind:

- Follow your ideas, publish your results and, most importantly, enjoy the exciting opportunities and new friendships afforded by a career in scientific research.
- Stick at it and don't give up through the hard times, especially when funding is precarious!

Professor Farquharson with members of his lab. © Farquharson



## Get set FOR GLASGOW



Get ready and reserve **19–21 November 2018** for this year's Society for Endocrinology BES conference! Join hundreds of your colleagues and friends to exchange knowledge, share experiences and and strengthen collaborations across our global community of endocrinologists.

### LECTURE HIGHLIGHTS

- Enjoy an exciting programme of **10 medal lectures** including:
- Starling Medal Lecturer **Leanne Hodson** (Oxford)  
*Hepatic fatty acid metabolism: the effect of metabolic and nutritional state*
  - Jubilee Medal Lecturer **Malcolm Parker** (London)  
*Ups and downs of nuclear receptor action*

### FUTURE SKILLS HIGHLIGHTS

- **Graham Leese** (Dundee)  
*How do I pass the SCE?*

### SERVICE IMPROVEMENTS

- **John Wass** (Oxford)  
*Getting it right first time (GIRFT) in endocrinology*
- **Helen Simpson** (London)  
*Optimising patient outcomes and time management: the perfect multidisciplinary team*

## SfE BES 2018 KEY DATES

Abstract deadline: **25 JUNE 2018**

Travel Grant deadline: **15 AUGUST 2018**

Early bird registration: **19 SEPTEMBER 2018**

Get the latest info:

[www.endocrinology.org/events/sfe-bes-conference/sfe-bes-2018](http://www.endocrinology.org/events/sfe-bes-conference/sfe-bes-2018)

Join the conversation: **#SfEBES2018**

### MEET THE EXPERT HIGHLIGHTS

- **Márta Korbonits** (London)  
*What the endocrinologist needs to know about genetics*

### SYMPOSIUM HIGHLIGHTS

- *Big data and bone disease*
- *Thyroid in pregnancy*
- Nurse symposia:  
*Pituitary adenomas: beyond surgery and Adrenal crisis and steroid education: raising the safety bar*
- *Early Careers: Navigating the academic pathway*

### UP FOR DEBATE...

#### Who do you think is right?

- *Brain vs gut - this house believes that the gut is the conductor of the endocrine orchestra*  
**For: Carel Le Roux** (London)  
**Against: Giles Yeo** (Cambridge)

### DISCOVER SOMETHING NEW!

#### Find out more at the Applied Physiology Workshops

- *Metabolites as hormones: new hormones everywhere*
- *GPCRs: hotspots and complexes*

### JUST A FEW OF OUR EXCITING TALKS

- *Metabolites as cell-to-cell signals*
- *Short chain fatty acid signalling in human health and disease*
- *Gut metabolites and human health*
- *The nanodomain organisation of GPCR signalling: lessons from thyrotrophin receptors and beyond*
- *FSH and thermogenesis*

### CLINICAL MANAGEMENT WORKSHOPS INCLUDE

- *Aggressive pituitary tumours*
- *Endocrine emergencies*
- *Treating troublesome menopausal symptoms*



# A chance to make your mark: ENDOCRINOLOGY IN THE MEDIA



You may never have considered it, but, by engaging with the media, you could help make a difference and improve the quality of news reporting across endocrinology. Your input could be crucial in ensuring that scientific accuracy is maintained, whilst real-world implications are explained responsibly.

Reports on scientific and health topics that lack independent, expert input may risk conveying a message that is misconstrued. This can be bad for public health – and have an even greater negative impact on the public's opinion of scientists and doctors.

The Society for Endocrinology aims to engage non-specialists with the impact and potential of endocrinology, and also to ensure that people recognise the Society as an authority in hormone science.

Achieving these aims involves disseminating expert information online and via the media.

The Society's Media Ambassadors are members who work with our press office, and you could join them. They provide expert insight and context regarding endocrinology-related news stories within their specialist areas.

Here are just a few examples of how these members helped to shape stories of endocrinology in the news for the better.

In 2017, expert opinion and reactions from the Society's Media Ambassadors helped shape more than 70 news stories. Since the beginning of 2018, they have contributed to at least 20 more.

## MAKING AN IMPACT ON ENDOCRINOLOGY REPORTS

1. In March, a study linking low thyroid levels to chronic fatigue syndrome was picked up by the media. Before the story broke, the BBC contacted the Society press office asking for expert opinion on the research. After **Simon Pearce** (Newcastle University) cautioned that the findings were not conclusive and could easily be misinterpreted, they decided to shut down the story.



Simon Pearce

2. A study presented at the Endocrine Society annual meeting linked essential oils to breast development in men. Society members/Media Ambassadors **Rod Mitchell** (University of Edinburgh) and **Ieuan Hughes** (University of Cambridge) added context to a BBC news article, by clarifying the caveats associated with extrapolating experimental data obtained in cells to humans.



Rod Mitchell



Ieuan Hughes

3. Society member/Media Ambassador **Channa Jayasena** (Imperial College London) provided expert comments on a study linking antihistamines to fertility problems in men for *The Guardian*. He pointed out that it was too soon to raise any alarms about these medications. BBC News also sought Channa's expertise in reproductive endocrinology when the story of the first reported case of a transgender women being able to breastfeed broke at the start of this year.



Channa Jayasena



Publicato il: 05/01/2018 14:06  
 Uno studio getta ombre sul paracetamolo usato nella gestione dell'infiammazione. Secondo alcuni studi condotti solo su animali durante la gravidanza potrebbe causare gravi conseguenze.

L'articolo esamina lo sviluppo alterato nei feti trattati con paracetamolo, potrebbero compromettere adulti.

Il paracetamolo, o acetaminofene, è un trattamento da banco usato per alleviare il dolore e ridurre la febbre. In questo articolo, David Kristensen e colleghi della University of Copenhagen, Danimarca, hanno condotto uno studio sugli animali sui feti. In questi studi, i ricercatori hanno scoperto che l'esposizione al paracetamolo durante la gravidanza potrebbe compromettere lo sviluppo dei feti e delle cellule che una donna trasmette ai propri figli.

The Society doesn't just respond to media stories with expert reactions – we also work proactively to highlight the latest innovative research in our journals.

## BY PROMOTING NOTEWORTHY RESEARCH TO JOURNALISTS, WE CAN INFORM A BROADER AUDIENCE ABOUT ADVANCES IN ENDOCRINE SCIENCE AND HEALTHCARE RESEARCH.

- In January, a review in *Endocrine Connections* by **David Kristensen** and colleagues (Copenhagen University Hospital) linked exposure to paracetamol during pregnancy and negative effects on the fertility of female offspring. It was released to the press by the Society press office, along with independent comments from our Media Ambassadors for journalists. Over 80 media stories were generated in 20 countries. Although an animal study, the implications of this research for public health were highlighted, along with the fact that further investigation is needed.



- Last December, **Phil Lowry** and **Russell Wood** (University of Reading) published research in *Journal of Molecular Endocrinology*, which also hit the news thanks to a Society press release. This work indicated how morning sickness may be the sign of a healthy pregnancy. UK newspapers jumped at the chance to reassure the Duchess of Cambridge, who was experiencing a severe form of morning sickness, that 'It was all OK'!

- During the Society for Endocrinology BES conference 2017 in Harrogate, the Society prepared a number of press releases on the exciting work that was being presented. One featured a study by **Janet Lord** and **Khaled Al-Tarrah** (University of Birmingham) on the potential of vitamin D to aid in burn healing. This really caught the media's attention and generated more than 150 stories worldwide. In addition, Professor Lord appeared on Health Check, a radio show on the BBC World Service.



Are you interested in sharing your expertise to help improve science and health reporting? Find out more about Media Ambassadors, and how to become one, at [www.endocrinology.org/outreach/public-engagement/opportunities](http://www.endocrinology.org/outreach/public-engagement/opportunities).



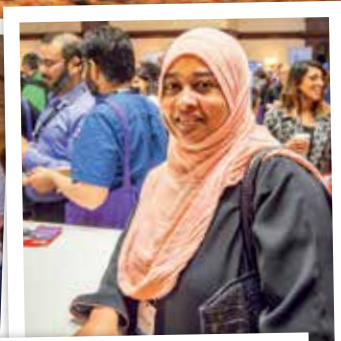
# Celebrating our first-ever **ENDOCRINE ACADEMY**



In April 2018, the Society held its inaugural Endocrine Academy. For the first time, Clinical Update, Endocrine Nurse Update and the Career Development Workshop took place concurrently, at the Hilton Birmingham Metropole NEC. Featuring combined lecture sessions and joint coffee and lunch breaks, the event offered delegates unique networking opportunities with colleagues across the discipline.

The individual components of the Endocrine Academy are designed to provide clinicians, scientists and nurses with an in-depth, tailored and up-to-date programme, while the joint sessions enable attendees to build relationships and collaborations with colleagues across endocrinology.

Take a look at our photo highlights for a flavour of this year's sell-out Endocrine Academy. We hope to see you at the next one!







## Endocrine Academy IN NUMBERS

### Clinical UPDATE

16-18 April

**209** delegates

**61** speakers

**30** workshops

### Endocrine NURSE UPDATE

16-17 April

**42** delegates

**14** speakers

**5** interactive sessions

### Career DEVELOPMENT WORKSHOP

16-18 April

**20** delegates

**6** speakers



Visit the Society's Facebook page to see more Endocrine Academy photos.



## JANET LEWIS: ENDOCRINE NURSE AWARD WINNER 2018



The Society's Endocrine Nurse Award recognises individuals who have demonstrated innovative and successful nurse-led initiatives in endocrinology, thereby advancing best practice in research, education or patient care.

The winner of the 2018 award is Janet Lewis of the University Hospital of Wales (UHW), Cardiff. Here, Janet tells us about her campaigning to improve care and reduce inequalities for patients with neuroendocrine tumours (NETs) in Wales.

Part of my endocrine specialist nursing role at UHW involves the care of patients with NETs. Our service for these patients developed quickly, and I began to see large numbers of metastatic gastrointestinal/bronchial and genetic NETs in my nurse-led clinic. It became apparent that patients were receiving inadequate and disjointed care, due to the location in which they lived. Those living in North Wales had access to a centre of excellence in Liverpool, but patients who lived outside the Cardiff area had to wait 6 weeks for a referral to our centre.

While the incidence and prevalence of NETs are low in comparison with other cancers, their effect and impact on patients and families are

*'Witnessing the injustice of the "postcode lottery", I felt compelled to raise awareness of NETs.'*

Janet Lewis (right) receives her award from Lisa Shepherd at Endocrine Nurse Update in Birmingham.



devastating. Most clinicians and surgeons may never come across NET patients in their career. Many patients received limited support from cancer charities, which lacked the knowledge and skills to guide the patient through their cancer journey. This left patients feeling isolated and lonely.

Witnessing the injustice of the 'postcode lottery', I felt compelled to raise awareness of NETs. I established a support group in Cardiff, with the help of Cathy Bouvier, Director of NET Patient Foundation, and some patients. Now our support group has 50–60 members. It has been a tremendous help to our patients by sharing experiences, as well as by offering support and education to individuals and their relatives.

The patients and I began to question why people with NETs were not recognised and treated in the same way as patients with other types of cancer, who have routine access to services, including a designated clinical nurse specialist (CNS). We researched the Welsh Cancer Delivery Plan, amongst other documents. This stated that all patients with cancer should have equal access to treatment, regardless of where they lived in Wales, with access to a CNS, of which the NET patients had neither.

This inspired us to network with other cancer charities and third-party sectors. We invited ourselves to cancer conferences and focus groups, to raise awareness of NETs. We sent patient stories to Welsh Assembly Members (AMs), Chief Executives of seven Health Boards and the Welsh Minister. We held an awareness event in the National Assembly for Wales on World NET day 2013, where Sally Jenkins (a NET patient) and Professor Steve Davies (consultant endocrinologist) presented a comprehensive case to the AMs. This was highly successful and we were invited to participate in the inquiry into implementation of the Welsh Government's Cancer Delivery Plan.

Through the strong support of the AMs who sat on the Committee of the Welsh Cancer Plan, the Health Minister agreed that NET services in Wales should be examined urgently. He instructed the Welsh Health Specialised Services Committee (WHSCC) to create a task and finish group, which included the Director of the NET Patient Foundation, patients, consultants and myself. The cancer planners and commissioners of the WHSCC were highly professional, very caring and understanding. They collated important statistics and information and as a group, we all worked in partnership, which led to a highly successful outcome. WHSCC agreed to commission NET services in Wales and funds were released centrally to develop the service.

The implementation of these recommendations is still in its early development, but patients now have access to the new NET service in Cardiff and NET centres of excellence in Liverpool and London, which provide pioneering treatments and PET gallium scans not currently available in Wales. Two designated NET CNSs have also been recruited to support patients.

This powerful partnership between patients and nurses has had a significant impact on patient care. The overall effect of these recommendations has been the commissioning of new services, leading to an improvement in the standard and equity of care for NET patients in Wales.

**JANET LEWIS**  
Endocrine Nurse Award Winner 2018

Applications are open for the 2019 Endocrine Nurse Award until 29 June 2018. See [www.endocrinology.org/grants-and-awards](http://www.endocrinology.org/grants-and-awards).

# SUBMIT YOUR ABSTRACTS FOR SfE BES 2018

'Nursing practice' is one of the categories for abstracts submitted to the Society for Endocrinology BES conference 2018, and all nurses are encouraged to submit at [www.endocrinology.org/sfebes2018](http://www.endocrinology.org/sfebes2018). The deadline for submission is **25 June**. Accepted abstracts are presented at the event as a poster, e-poster, or as an oral presentation, and will also be published online in Endocrine Abstracts.

Please contact [zoe.plummer@endocrinology.org](mailto:zoe.plummer@endocrinology.org) for further information or support (including examples of previous nursing abstracts and posters). Advice on writing abstracts was given at the recent Endocrine Nurse Update and is also included on these pages, as attendees said they found it useful.

## HOW TO WRITE A SCIENTIFIC ABSTRACT

An abstract might relate to a conference poster or an oral presentation. Its aim is to provide the reader with a brief summary, outlining a piece of work undertaken or in progress. The poster or presentation will then offer much more detail for those who are interested in knowing more.

Divide your abstract into the following sections:

### 1. Introduction (one to two sentences)

- (a) Why was the work done?
- (b) What was the aim of the work?

### 2. Methods

- (a) How were data gathered?

- (b) Include information about sample size, data collection methods, etc.

### 3. Results

- (a) What did the study find out?
- (b) Did this match the original theory?

### 4. Discussion (one to two sentences)

- (a) How does the outcome affect service delivery/development?
- (b) Will it be repeated to review service changes?

It is important to stick to the word limit provided and ensure authorships are annotated according to guidelines provided by the event organisers.

**Example abstract:** Little Miss Muffet – Arachnophobe or drama queen?

Section	Subsection (not published)	Abstract (as published) (237 words)
Introduction	Why was the work done?	This work was undertaken to establish why Little Miss Muffet (LMM) was unable to remain in the presence of a spider
	The aim of the work	The aim was to identify the fears/concerns of LMM and enable development of strategies for improving self-management
Methods	How were data gathered?	In order to provide objective and subjective data two methodologies were utilised. Firstly, direct observation of LMM when exposed to an arachnid under controlled conditions provided visual evidence of reaction. This included monitoring of vital signs and measurement of biochemical stress markers.
	Information about sample size, etc.	Secondly, the subject was interviewed using a mix of open and closed questioning to ensure more subjective concerns could be expressed. The responses were then gathered into themes such as childhood experiences, parental influence and peer pressure
Results	What did the study find out?	The results of both objective and subjective methods confirm that LMM is arachnophobic and that hunger does not suppress this. Her fear is genuine to her and treatment plans developed reflect this
	Did this match the original theory?	The outcome did demonstrate our hypothesis that LMM is arachnophobic; however, more detailed analysis established this fear is a learned behaviour giving more potential for resolution with appropriate therapies
Discussion	Does the outcome affect service delivery?	Establishing the basis for LMM's fear of spiders has meant a moderate adjustment in care delivery – services can be more focused and more sensitive in supporting LMM in continuing her current care whilst addressing her arachnophobia by desensitisation therapy and neuro-linguistic programming.
Conclusion	Will it be repeated?	The intention will be to review progress by repeating the investigations within a 6- to 12-month period.

# HOW TO APPLY FOR: THE SOCIETY'S ENDOCRINE NURSE GRANT

## SUMMARY OF COSTS

You need to provide a breakdown of how you plan to spend the awarded money, including a short explanation of why you need each item.

## JUSTIFICATION FOR FUNDING

So that the marking panel can understand the motivations behind the project, a justification for the grant is needed. The justification should include some consideration of three broad areas:

- the benefit to the applicant
- the benefit to the endocrine practice and community
- how findings will be shared.

### 1. Benefit to applicant

The Society aims to support all its members to achieve their potential, so it is important to include information on the personal benefit the grant could bring. This should include what your professional goals are, and how undertaking the funded project will help you in progressing towards these goals.

#### Examples:

- Taking on a leadership role at some point in the future
  - leading an audit can allow you to prove you can identify problems, propose solutions, identify their suitability and evaluate the outcomes
- Apply for a PhD
  - Having preliminary data as part of your PhD application can increase the chance of success
  - The skills you learn undertaking a short research project will be applicable to your PhD
- Increasing specialisation in an endocrine area

### 2. Benefit to endocrine research/nursing/clinical practice

Your project will offer some benefit to the wider endocrine community. It is important to explain why these benefits matter, and how your funded project will provide improvements. Identifying what gave you the idea to undertake the project can be helpful here. While your project will offer benefit to endocrine practitioners, it should also improve the experience of patients and their carers. For some projects this impact may be direct and easy to identify, for others the impact may be more indirect.

#### Examples:

- Testing whether a new approach is cost-effective
- Helping to build a climate for nurses to become more autonomous
- Reducing pressure on consultant clinics
- Helping ensure continuity of care
- Quicker diagnosis or access to medication
- Ensuring safe and quality care for patients
- Reducing patient waiting times

### 3. How findings will be shared

Even the greatest of projects will have little impact if the findings/learning are never shared. It is important to consider how you hope to share your findings after completing your project.

#### Examples:

- Publishing a paper in a peer reviewed journal such as *Endocrine Connections*
- Presenting a poster or talk at a conference such as SfE BES or RCN
- Sharing your findings at Endocrine Nurse Update
- Making use of communication channels within your institution

## EXAMPLES OF REAL PROJECTS

### Outcome of patients with Graves' disease after long-term follow-up

Audit of the outcome/relapse rate and possible predictive factors of recurrence in a series of patients with Graves' disease managed in a nurse-led thyroid clinic. To achieve this, notes were reviewed for 60 patients with newly diagnosed Graves' disease seen in the clinic between 2005 and 2011 and who had completed 18 months of anti-thyroid drug treatment.

[www.endocrine-abstracts.org/ea/0028/ea0028p157.htm](http://www.endocrine-abstracts.org/ea/0028/ea0028p157.htm)

### A thyroid nurse-led service: patients' perspective: an audit

A thyroid, nurse-led clinic (NLC) was set up in the Department of Endocrinology in Oxford primarily to reduce waiting times of patients with uncomplicated thyrotoxicosis from 3–4 months to 2–4 weeks. An audit explored the patients' perspective on the provision of care and the service delivery. A structured questionnaire was created to perform the audit: 22 questions examined patients' views on care and management, nurse's knowledge and skills, efficiency of the service, and possible concerns. This was posted to the first 40 patients, who had been seen in the thyroid NLC. All data were collected anonymously. Thirty questionnaires were returned over 4 weeks. This gave a valuable insight into understanding patients and the success of the service.

[www.endocrine-abstracts.org/ea/0019/ea0019p392.htm](http://www.endocrine-abstracts.org/ea/0019/ea0019p392.htm)

There are two application deadlines for the Endocrine Nurse Grant per year, the next is on **Wednesday 28 November**. More details are available at [www.endocrinology.org/grants-and-awards](http://www.endocrinology.org/grants-and-awards).

## LISA SHEPHERD

### NURSE COMMITTEE CHAIR



I would like to start by thanking Janet Lewis, from University Hospital Wales in Cardiff, for writing for us in this issue. Janet was awarded the Society's second Endocrine Nurse Award, in recognition of her incredible work in the development of equitable services for neuroendocrine tumour (NET) patients. Janet's determination led to the commissioning of a NET service in Wales. It demonstrates the positive impact nurses, in collaboration with patient support organisations, have in improving the care of patients.

So many nurses do outstanding work like Janet's that often goes unrecognised. Please take time to nominate yourself or a colleague for the prestigious Endocrine Nurse Award. A link to further details can be found on page 28.

The Society for Endocrinology BES conference 2018 takes place on 19–21 November in Glasgow. We encourage all nurses to submit an abstract: the deadline is 25 June. This would enable you to disseminate your nursing practice and research to your peers, either by means of a poster or an oral presentation. If you think the preparation of an abstract looks like a major undertaking, remember that help and support are available from the Society for Endocrinology and your colleagues, including the Nurse Committee. Useful information can also be found on these pages.

Finally, don't forget the Society for Endocrinology Endocrine Nurse Grant is available for nurses who wish to undertake an audit or piece of research. More information is provided here to help you apply.

I wish you all a pleasant, and hopefully relaxing, summer.

LISA SHEPHERD



# MARGARET H I DODD (1921–2017)



Endocrinology lost a person of distinction when Margaret Dodd died at the age of 96 in December 2017. In so many ways, her life and career reflected changes in the 20th century. She was born Margaret Greig just after the end of the Great War, and was amongst that small percentage of women who attended university, in her case Aberdeen. She graduated in the midst of World War II, and like so many of her generation, she promptly married. Her husband, Ian Macauley, was later killed in that conflict.

## EARLY DAYS IN RESEARCH

As a young scientist she worked with Frank Landgrebe and Harry Waring at Aberdeen, and they published the seminal paper on the vasopressin bioassay using blood pressure in rats,<sup>1</sup> a familiar method used by those of us raised in the 'bioassay generation'. Landgrebe went on to the Medical School in Cardiff, whilst Harry Waring emigrated to Western Australia, and is credited as leading those who decided that Australian native species were more interesting to study than white rats.

Margaret herself was awarded a prestigious Henry Fellowship and went to Radcliffe College (Cambridge, MA, USA), in those days the female counterpart to the then all-male Harvard, and now part of the world's finest university.

## WORKING AS A DUO

After her return, she began working in amphibian endocrinology. In 1951, she married James (Jimmie) Dodd, and from then onwards they worked as a duo, but Margaret was never properly rewarded with a full-time academic post. This says much about how bad the situation was for university women all over the world, a defect only repaired relatively recently.

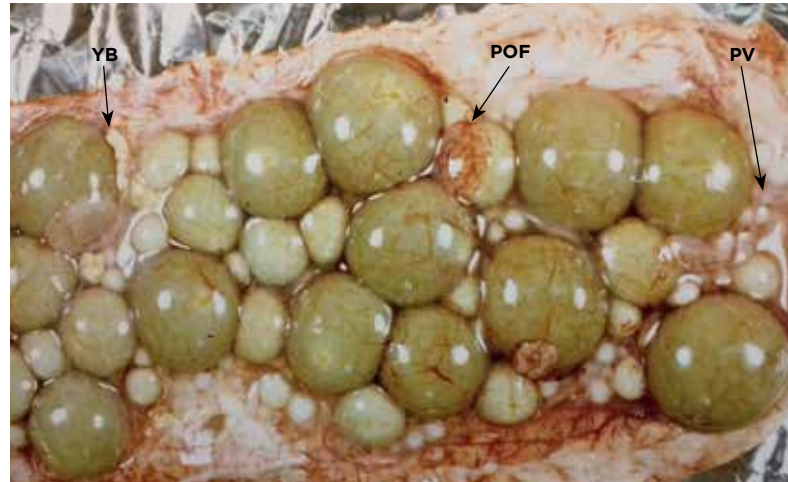
The Dodds moved from St Andrews to Leeds, where Jimmie was Head of Zoology for 8 years, and then to the University College of North Wales (now Bangor University), where he led Zoology until his retirement at the statutory age of 67. Sadly, he died 4 years later. Margaret moved to Warwickshire in her retirement.

Throughout all these years Margaret maintained her research as well as bringing up their splendid family of three boys: Chris, Nick and Peter.

## HER TWO AREAS OF RESEARCH

### Amphibian metamorphosis

Margaret and Jimmie studied metamorphosis in all its aspects, using tadpoles of *Xenopus laevis*. This was a convenient model species, since the adults were available in most hospitals, as they were used for pregnancy diagnosis in humans until the advent of radioimmunoassay. Metamorphosis remains a fascinating phenomenon and is largely dependent upon thyroid hormones. The Dodds focused especially upon the hypothalamic-pituitary control of thyrotrophin release and summarised the situation in a lengthy and detailed review article.<sup>2</sup> Much more detail can be found in Jimmie Dodd's *Biographical Memoir*.<sup>3</sup>



The dogfish ovary. Hundreds of oocytes are visible. PV is an area of pre-vitellogenic follicles (no yolk and <7mg) many of which later become vitellogenic and filled with green-yellow yolk (2.5–3.0 g). POF indicates a post-ovulatory follicle with only the blood vessels remaining visible. YP are even older atretic follicles from the previous reproductive season. January 1977, MHI Dodd

## Elasmobranch reproduction

A primary reason for their move to Bangor in 1968 was the ready availability of marine facilities, and specifically large numbers of the lesser-spotted dogfish (*Scyliorhinus canicula*). Margaret and Jimmie focused especially upon reproduction, and the accompanying image shows the ovary of a mature dogfish (taken in January 1977). The scale of vitellogenesis and the green-yellow maturing follicles are striking. There is more detail in the *Biographical Memoir*<sup>3</sup> and I found hundreds of electron micrographs of the dogfish ovary during vitellogenesis and follicular growth when looking at her papers. How Margaret would have revelled in our present age, when the entire genomes of both her beloved species are available to answer so many questions.

## FINAL REFLECTIONS

Margaret was a deeply intellectual woman who supported organisations dedicated to helping people who are deprived: it was moving to see those memberships in her memorabilia.

Let me end though on a happy note. I smile when recalling the chaotic months after we had arrived in Bangor. Light relief came from across the corridor, and I can still hear today the merry laughter in 1969, as Margaret and Jean Joss (Macquarie University, Sydney, NSW, Australia; at that time completing her PhD on lampreys) worked away on thyroid hormones and metamorphosis. That was a period when undertaking research was discovery combined with fun!

## SIR BRIAN K FOLLETT

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2. Dodd MHI & Dodd JM 1976 In *Physiology of Amphibia* (Ed B Lofts), vol 3, pp 467–599. New York: Academic Press.
3. Sumpter JP & Follett BK 1991 James Munro Dodd FRS *Biographical Memoirs of Fellows of the Royal Society* **37** 129–147.



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Please refer to the full Summary of Product Characteristics before prescribing.

**Presentation:** Tostran 2% Gel, contains testosterone, 20 mg/g. **Indication:** Testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests. **Dose:** The starting dose is 3 g gel (60 mg testosterone) applied once daily to clean, dry, intact skin, on the abdomen or to both inner thighs. Adjust dose according to clinical and laboratory responses. Do not exceed 4 g of gel (80 mg testosterone) daily. Apply after washing, bathing or showering. Do not apply to the genitals. Do not use in women, or children under the age of 18 years. **Contraindications:** Known or suspected carcinoma of the breast or the prostate; hypersensitivity to any of the ingredients. **Special warnings and precautions for use:** Not to be used to treat non-specific symptoms suggestive of hypogonadism

if testosterone deficiency has not been demonstrated and if other aetiologies have not been excluded. Not indicated for treatment of male sterility or impotence. Monitor testosterone at regular intervals. Adjust dose to maintain eugonadal testosterone level. Experience in patients over 65 years is limited; caution for lower serum testosterone with increasing age. Pre-examine all patients to exclude a risk of pre-existing prostatic cancer. Perform regular monitoring of breast and prostate. Androgens may accelerate the development of subclinical prostatic cancer and benign prostatic hyperplasia. Use with caution in thrombophilia due to risk of thrombosis. Monitor haemoglobin, and haematocrit, liver function tests and lipid profile during long-term use. Oedema with/without congestive heart failure may be a severe complication in patients with pre-existing severe cardiac, renal, or hepatic insufficiency or ischaemic heart disease. Discontinue immediately if such complications occur. Use with caution in hypertension, epilepsy, migraine and sleep apnoea as these conditions may be aggravated. Care should be taken with skeletal metastases due to risk

of hypercalcaemia/hypercalcaemia. Androgen treatment may result in improved insulin sensitivity. Inform the patient about the risk of testosterone transfer and give safety instructions. Health professionals/carers should use disposable gloves resistant to alcohols. **Side-effects:** Very common: Application site reactions (including pruritus, xerosis, pruritis, rash or erythema). Common: Increased haemoglobin, red blood cell count, and haematocrit. Increased male pattern hair distribution. Hypertension, gynaecomastia, peripheral oedema, and increased PSA. May cause irritation and dry skin. Prescribers should consult the summary of product characteristics for further details of side effects. **Legal Category:** POM. **Further information is available from the Marketing Authorisation Holder: Kyowa Kirin Ltd, Galahack Business Park, Galahack, TD1 1QH, UK. Date of Prescribing Information:** March 2017.

For the United Kingdom: Pack Size and Price: Pack contains one 60 g metered-dose canister. Price £28.67. **Marketing Authorisation Number:** PL14500/0025.

Adverse Events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard). Adverse events should also be reported to Kyowa Kirin Ltd on +44 (0)1896 664000, email [medinfo@kyowakirin.com](mailto:medinfo@kyowakirin.com)

**References:** 1. Tostran® Summary of Product Characteristics. 2. eMIMS January 2018. 3. Morgentaler A, et al. Steady-state pharmacokinetics. SMSNA Annual meeting 2011.

Date of preparation: January 2018. Job code: UK/M015/0507

**KYOWA KIRIN**

